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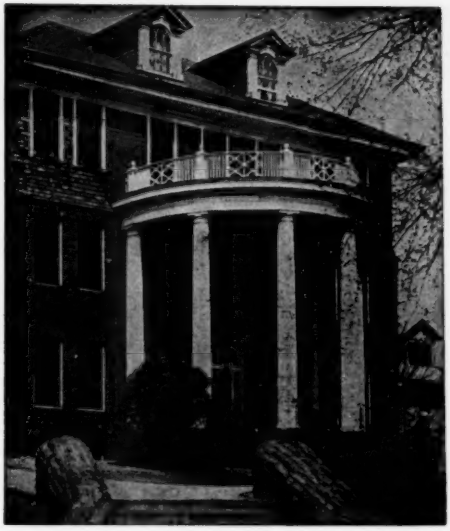

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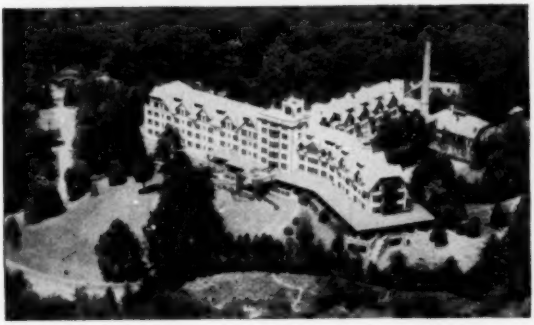

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NEW CONCEPT OF CRITICAL STEPS IN COURSE OF CHRONIC DEBILITATING NEUROLOGIC DISEASE IN EVALUATION OF THERAPEUTIC RESPONSE

A Longitudinal Study of Multiple Sclerosis by Quantitative Evaluation of Neurologic Involvement and Disability

LEO ALEXANDER, M.D.
BOSTON

THE EVALUATION of response to therapy in multiple sclerosis is complicated by well-known difficulties (Brickner,[1] Putnam,[2] and Schumacher [3]). One of these is the frequently noted discrepancy between the extent of recovery of individual signs and symptoms (e. g., reflexes, strength) and the degree of change in the over-all disability status, as expressed most strikingly by the quality of locomotion, as well as by the ability to carry out other complicated tasks.

It is not uncommon to find a comparatively small amount of improvement in individual signs and symptoms associated with a great deal of improvement of over-all disability status, and, conversely, fairly significant degrees of improvement in individual signs and symptoms failing to be reflected in commensurate improvement in the over-all disability status. It is tempting—and sometimes valid—to consider this discrepancy as due to the fluctuations of emotional overlay; but this is by no means so in all cases, since the discrepancy has been observed in patients in whom emotional overlay was practically absent, whereas with other patients the trend has proved to be independent of that of the emotional overlay.

This problem, namely, that of the frequent discrepancy between the extent of recovery of individual signs and symptoms and the degree of change in the over-all disability status, seemed to me early in my clinical work with multiple-sclerosis patients to be explainable in quantitative terms (Alexander [4]). A systematic large-scale approach to the quantitative problem, however, could not be envisioned until Mr. Chandler Hovey, chairman of the Massachusetts Chapter of the National Multiple Sclerosis Society, suggested devising a method that would lend itself to graphic representation of the course of the total illness in each patient, and of the

From the Neurobiologic Unit and the Multiple Sclerosis Research Clinic, Boston State Hospital.

Supported by a grant from the Massachusetts Chapter of the National Multiple Sclerosis Society.

1. Brickner, R. M.: A Critique of Therapy in Multiple Sclerosis, Bull. Neurol. Inst. New York **4**:665 (April) 1936.

2. Putnam, T. J.: The Criteria of Effective Treatment in Multiple Sclerosis, J. A. M. A. **112**:2438 (June 17) 1939.

3. Schumacher, G. A.: Multiple Sclerosis and Its Treatment, J. A. M. A. **143**:1059-1065 (July 22), 1146-1154 (July 29), 1241-1250 (Aug. 5) 1950.

4. Alexander, L.: The Element of Psychotherapy in the Treatment of Organic Neurologic Disorders, J. Nerv. & Ment. Dis. **111**:336-343 (April) 1950.

course of the illness in groups of patients, including total clinic populations. The dearth of quantitative information in the literature has, in fact, been one of the most striking drawbacks of the published work on therapy in multiple sclerosis. It seemed

TABLE 1.—*Weighting Chart*

Vision	
Corrected: Less than 20/200	20
20/200-20/100	15
20/70-20/50	10
20/40-20/25	5
Pupils	
Pupillary asymmetry	2
Abnormal reaction to light or in accommodation	5
Eye Movements	
Marked (such as ocular muscle palsies or diplopia)	10
Moderate or slight (such as disturbance of convergence)	5
Nystagmus	5
Tongue—Deviation	2
Facial Signs	
Asymmetry: Marked	5
Slight	3
Optic Disks	
Pallor: Marked	15
Moderate	10
Minimal or slight	5
Blurring	10
Visual Fields	
Restricted: Marked	15
Moderate	10
Minimal or slight	5
Scotoma (not to be scored if vision is less than 20/200)	10
Speech	
Defect: Marked	15
Moderate	10
Minimal or slight	5
Posture	
Inability to stand	15
Abnormal: Marked	10
Slight	5
Status	
Bedridden	20
Wheel chair	15
Walking with support of other person	10
Crutches	8
Cane	7
Walking unaided with abnormal gait	5
Coordination	
Disturbance *: Marked	10
Moderate	5
Minimal or slight	2
Adiadokokinesis	
+	5
Slight or ±	2
Romberg Sign	
+	10
±	5
Strength †	
Paralysis	20
Weakness: Marked	15
Moderate	10
Slight	5
Tonus ‡ (Increased or decreased)	
Marked	15
Moderate	10
Slight	5
Abnormal Movements	
Marked	10
Moderate	5
Slight	2
Tendon Reflexes	
+++	1
++++	2
Absent	2
Clonus	
+ ++ +++	4
±	3
Mayer Sign	
0	2
Hoffmann	
+	5
±	3
Abdominal Reflexes (per side)	
Absent	15
Partially preserved	10
Exhaustible	5
Cremasteric Reflexes (per side)	
Absent	15
±	10
Babinski Sign (per side)	
+	20
±	10
Absence of Plantar Reflex Without Babinski Sign	5
Other Abnormal Toe Phenomena each	5
Sphincter Disorders	
Incontinence	20
Occasional incontinence	10
Retention	10
Frequency	5
Urgency	5
Difficulty in starting stream—occasional retention	5
Sensation (per side, per quality)	
Absent	10
Diminished	5
Hyperesthesia or focal pain	10
Paresthesia or subjective numbness	5
Impotence	15
Other Significant Signs, e. g.	10
Exophthalmos due to retrobulbar neuritis with pain in eyeball	
Temperature differences	
Paravertebral spasm	

* Disturbances of coordination are scored as follows: One combined score is given for ataxia, intentional tremor, and dysmetria, but separate scores are given for each arm and leg and for performance with eyes closed and for performance with eyes opened, i. e., for finger-to-nose test, finger-to-object test, knee-to-heel test, and for toe-to-object test. One combined score for each side is given for bradyteleokinesis; one, for static tremor, and one, for tremor at rest.

† Strength is scored for extension and flexion of each important group of muscles separately. Muscle groups are distinguished for the hip, knee, foot, shoulder, elbow, and hand grip (together with the wrist—no separate score for the wrist). Thus, a complete triple flexion paralysis of the leg would be scored 60; moderate weakness of extension of one hip, 10; marked weakness of grip on one hand, 15, or slight weakness of extension of one wrist, 5.

‡ Tonus is scored for each extremity.

worth-while, therefore, to investigate this particular problem of the quantitative features of the disease and to attempt to formulate some sort of weighting system for neurologic signs and symptoms, in an effort to analyze degrees of involvement and subsequent improvement by totaling such quantitative evaluations.

PRESENT INVESTIGATION

Specifically, the present study is based on the clinic population of the Boston Multiple Sclerosis Research Clinic, which is part of the neurobiologic unit of the Boston State Hospital. This population is comprised at present of 402 patients, 212 of whom live near enough to the hospital to allow frequent examinations either at the clinic or in the patient's home. These patients have been subjected to intensive study, with frequent complete reexaminations at intervals averaging three months.

The present paper is based on the examinations and reexaminations quantitatively scored according to the weighting system finally evolved. My purpose is to illustrate the use of such a system in charting and evaluating three factors of prime importance in further research in multiple sclerosis, and presumably in similar chronic debilitating diseases of the nervous system: (1) the changing status of the disease in individuals and in groups, i. e., a longitudinal study of the course of the disease in individual patients and in groups of patients; (2) the quantitative aspects of improvement, irrespective of whether it be spontaneous or in response to various types of therapy, and (3) the resulting concept of critical steps or levels in recovery or decline.

The Weighted-Sign System.—After a good deal of trial and error, a weighting system and resulting scoring method were finally arrived at which appeared to reflect adequately the state of the disease and its fluctuations in individual patients. It is comprised of score values assigned to significant variables of the disease, weighted according to the importance of the variable (Table 1). Normal findings are given a score of 0, while the various degrees of neurologic involvement are weighted from —1 to —20. Thus, high scores are given to signs of relatively great heuristic value, while relatively low scores are assigned to items which either are less important or meaningful or are not necessarily representative of the organic state, being, instead, subject to fluctuations of emotion, energy level, or motivation. With this method, a patient without neurologic abnormalities would receive a score of 0, while the maximum score of a totally disabled patient ranges down to —500 points.

For the past three years careful records of all neurologic examinations have been kept on a standard form, in order to ensure the patient's being subjected to uniform scrutiny. This form includes approximately 50 major items and requires the examiner to indicate the degree of severity of involvement. Those examinations recorded before my weighted-score system was evolved have been found to be sufficiently detailed to allow scoring by the new system.

The abnormalities found, after being recorded on the standard examination form, were then scored according to the weighted-sign list (Table 1), allowing a choice of about 100 different scores. These individual scores were then summed, the total score being considered representative of that particular examination, and this sum total was entered in an individual graph kept for each patient. Connecting lines between the points representing subsequent examination scores graphically illustrate the course of the disease in each individual patient. Up to the present, a total of some 700 examinations of 150 patients have been scored and graphed.

The total score for each examination, computed in this way, has been found to correlate well with the total clinical evaluation of the patient—that is, to be significantly related to his over-all clinical status—and it has proved of further value by illustrating the course of the disease in time under varying conditions and by leading to the development of a concept of critical levels of neurologic involvement. These points will be further elaborated later.

Relation of the Score to the Over-all Disability Status.—Score values were determined for 150 neurologic examinations carried out on 22 patients over a two-year period, the examining and scoring being done by one person (L. A.). The score values thus determined were then grouped under seven major disability categories based on a very important criterion of the disability status—the amount of restriction of the ability to get around: (1) patients walking with normal coordination; (2) patients walking unaided but with abnormal gait; (3) patients walking with the aid of a cane; (4) patients walking with support of another person; (5) patients using crutches; (6) patients confined to a wheel chair, and (7) patients who were bedridden.

It will be noted from the weighted-sign sheet (Table 1) that the disability category itself did not greatly influence the score values, since a score given for disability status itself varied only from —5 points, for walking unaided but with abnormal gait, to a maximum of —20 points, for

being bedridden. Thus, the total score was mainly determined by the sum total of the entire disability, in addition to the significant reflex abnormalities. While the score is weighted somewhat heavily for spastic paraplegia, this is in accordance with the fact that spastic paraplegia is the main source of disability in this disease. Severe ataxia is also heavily reflected in the score, incoordination being scored for each limb, separately for coordination tests with eyes open and with eyes closed, as well as for such separate items as adiadokokinesis, posture, Romberg's sign and spontaneous abnormal movements.

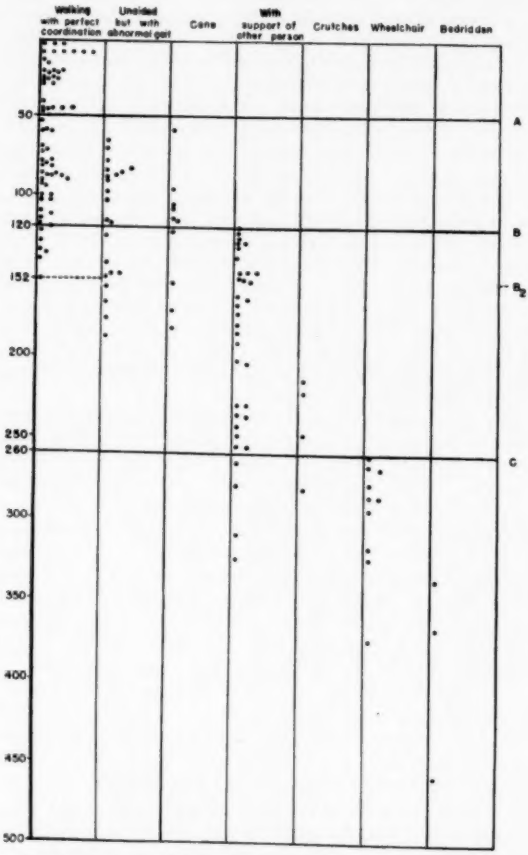

Chart 1.—Score values of 150 neurologic examinations of 22 patients, extending over a two-year period. All examinations were carried out by one examiner (L. A.) and scored by the same examiner. *A* indicates upper critical level; *B*, middle critical level; B_2, accessory critical level; *C*, lower critical level.

Above the level designated as —50 (Chart 1)—the count beginning at the zero line at the top of the graph and falling to —500 points at the bottom—no abnormalities of gait whatsoever were noted in this group; that is, patients whose ratings fell between 0 and —50 all walked with normal coordination. Below the level of —50, various degrees of abnormality of gait were found, but no patient whose rating fell above —120 was in need of another person's support when

walking. The lowest level at which any patient could still walk normally was —152. No patient above the level of —260 was in need of a wheel chair or was bedridden.

Another group of examinations, 400 on 78 patients, also carried out over a two-year period, but by four different examiners, and scored by four different assistants, was then similarly subdivided (Chart 2). Remarkable agreement was found between the two composite graphs (Charts 1 and 2). In the second group there was, for instance, only one patient with a score

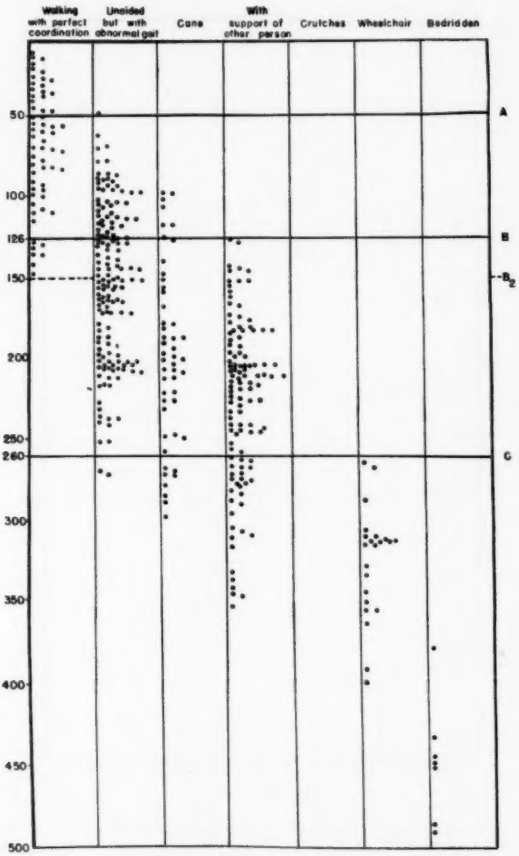

Chart 2.—Score values of 400 examinations of 78 patients, extending over a two-year period. The neurologic examinations were performed by four different examiners and scored by four differently trained assistants. *A* indicates upper critical level; *B*, middle critical level; B_2, accessory critical level; *C*, lower critical level. Note similarity of critical levels to those shown in Chart 1.

slightly above the level of —50 (namely, —48) who showed abnormality of gait; all other patients with scores above the —50 level walked with perfect coordination. Above the level of —126 no one needed the assistance of another person, while below the level of —150 no patient could walk normally. No patient above the level of —260 was wheel-chair-bound or bedridden.

Thus, from these data three major critical levels emerge. The upper critical level (*A*), falling at about —50 (—48 to —58), is that above which no abnormalities of gait were noted. The middle critical level (*B*), falling at about —120 (—120 to —126), is the one above which no patient needed the support of another person while walking. An accessory critical level (B_a), found at about —150 (—150 to —152), was the point below which no patient could walk with normal coordination. The lower critical level (*C*), falling at —260, indicates the point above which no patient was confined to a wheel chair.

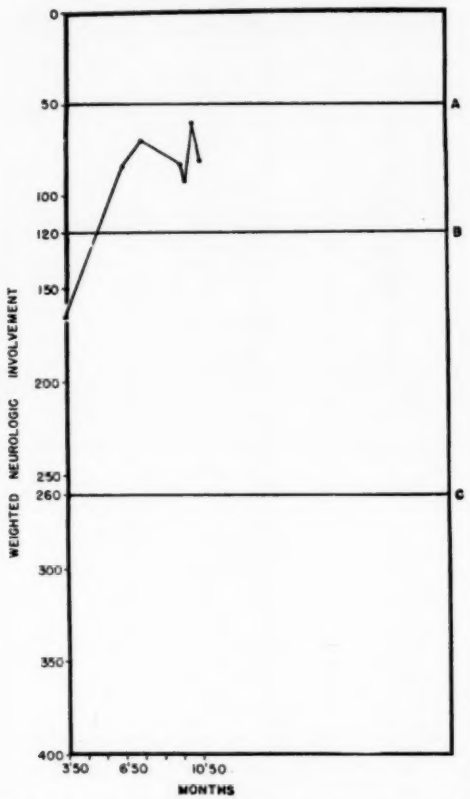

Chart 3.—Graphic representation of course of illness of a woman aged 25 over a seven-months' period, on a regimen of psychotherapy, allergen-free diet, and vitamins. Duration of illness was 18 mo. at beginning of observation.

USE OF THE SCORE IN ILLUSTRATING THE LONGITUDINAL COURSE OF THE DISEASE

Quantitative evaluation of the status of the patients by means of the rating scale at the outset of observation or therapy and that after completion of therapy has proved a great aid in realistic evaluation of response to therapy and of improvement in this disease.

Chart 3 illustrates the course of the disease in a patient who came under observation in March, 1950, after having had multiple sclerosis for 18 mo. At the time of admission her examination score was —164. Within the first four months of observation she improved 94 points; by that time she walked unaided and with only minimal ataxia on turning. Her graph reflects rather faithfully the relative quantitative amount of improvement. It is of particular interest that she experienced great

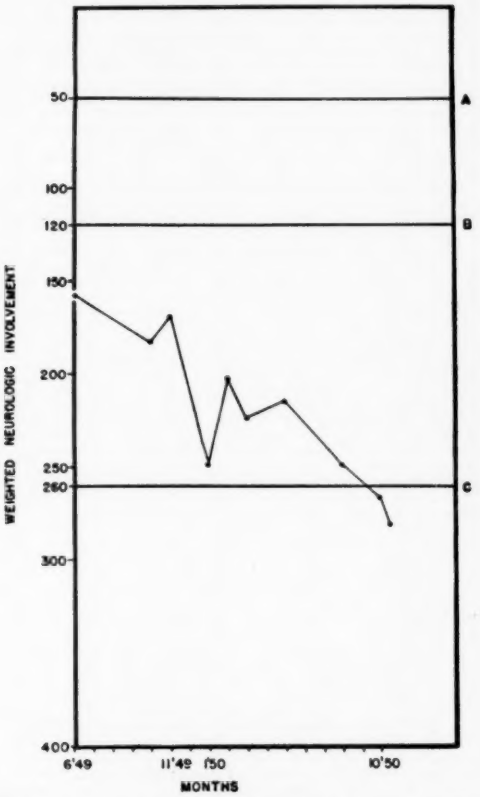

Chart 4.—Graphic representation of course of illness of a man aged 33, showing consistent decline over 17 mo., on the same regimen as that of the patient shown in Chart 3. Duration of illness was two and one-half years at the beginning of observation.

subjective improvement and marked improvement of function in the middle of the second month of clinic observation, at about the time the graph indicates that she crossed the middle critical level, assuming an even rate of progress at that time.

Another patient (Chart 4), who had been sick for two and one-half years at the outset of clinic observation, showed consistent decline on a similar regimen of therapy. His score was —158 at the outset. He was wheel-chair-bound and had to be hos-

pitalized shortly after he crossed the lower critical level at —260, 16 mo. later. This graph also illustrates an important feature shown by all patients with chronic progressive disease, namely, a continuing process of gradual attrition apart from specific attacks.

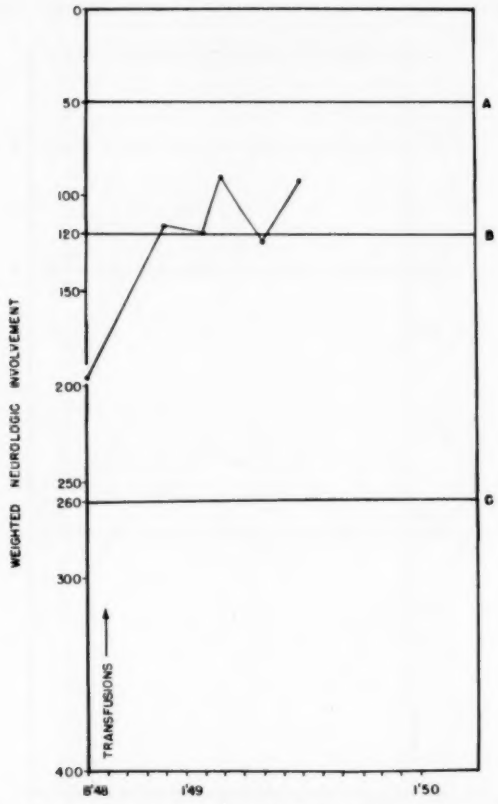

Chart 5.—Graphic representation of course of illness of a man aged 28, showing significant clinical improvement following blood transfusions. (Case 20 from Alexander, Loman, Lesses and Green.[5]) Note that the patient's graph crossed the middle critical level (*B*). Duration of illness was five years at beginning of observation.

QUANTITATIVE ASPECTS OF CLINICALLY SIGNIFICANT IMPROVEMENT VERSUS CLINICALLY INSIGNIFICANT IMPROVEMENT

From the 700 examinations of 150 patients so far scored and graphed, 100 graphs of 100 patients were selected at random for evaluation, and these form the basis of this section of the study. Among these 100 patients, clinically significant improvement or remission occurred in 36 instances in 34 patients, while clinically insignificant improvement occurred in 33 instances in 27 patients. The clinical significance

of improvement was assessed prior to the determination of the score rating and was based entirely on over-all clinical criteria.

As in a previous publication (Alexander, Loman, Lesses, and Green [5]) clinically insignificant improvement was defined as the definite improvement of neurologic signs or symptoms without, however, significant lessening of the patient's over-all

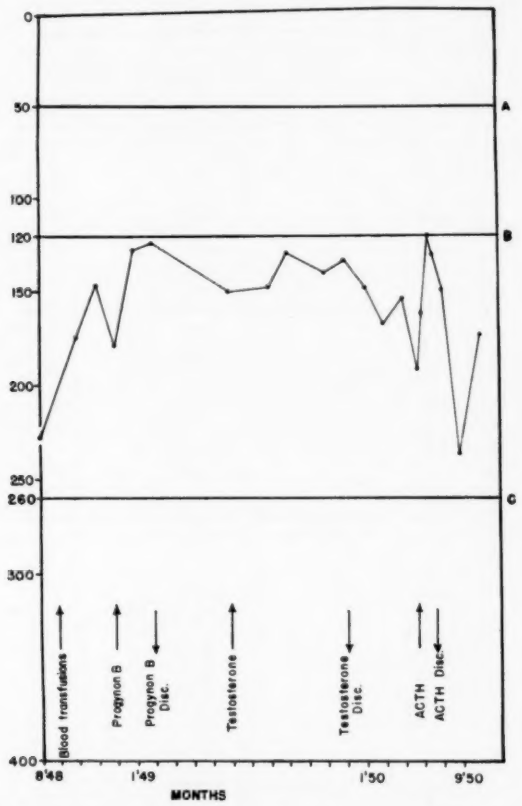

Chart 6.—Graphic representation of course of illness of a woman aged 51 over 26-mo. period, showing insignificant clinical improvement following blood transfusion, α-estradiol benzoate ("progynon-B"), testosterone, and, finally, corticotrophin. (Case 34 from Alexander, Loman, Lesses and Green.[5]) Note that the patient's graph never crossed the middle critical level (*B*). Duration of illness was 15 yr. at beginning of observation.

disability status. Clinically significant improvement was considered to have occurred when the patient achieved a remission or other significant improvement, not only

5. Alexander, L.; Loman, J.; Lesses, M. F., and Green, I.: Blood and Plasma Transfusions in Multiple Sclerosis: Multiple Sclerosis and the Demyelinating Diseases, A. Res. & Nerv. & Ment. Dis., Proc. (1948) **28**:178-200 (Feb.) 1950.

of neurologic signs or symptoms, but also of total disability status. Differentiation of the two groups was made on the basis of the clinical examination by the neurologist, the evaluation of the patient's social functioning by the social worker, and, to a less extent, the patient's subjective evaluation of his own capacities.

Depending on the clinical and social evaluation of the patient, he was placed in one of four categories: clinically significant improvement, clinically insignificant

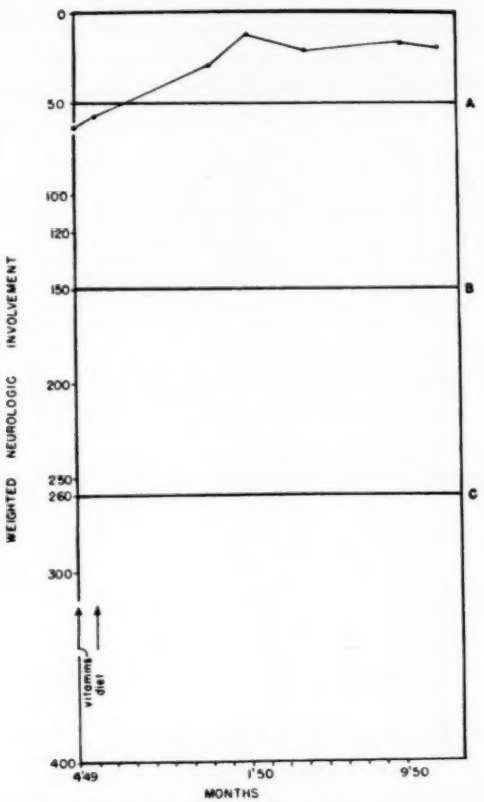

Chart 7.—Graphic representation of course of illness of a woman aged 33, showing significant clinical improvement on a wheat-free diet. Note that the patient's graph crossed the upper critical level (*A*). Duration of illness was two and one-half years at beginning of observation.

improvement, condition unchanged, or condition worse. After this purely clinical evaluation, the score values were determined for each patient. When the total scores for the first two groups (patients with clinically significant improvement and patients with clinically insignificant improvement) were compared, it was found that the clinical significance of improvement was not a function of quantitative gain in point

score alone but, rather, depended on whether or not the gain succeeded in pushing the patient across a critical level.

The patient whose graph is shown in Chart 5 achieved clinically significant improvement after a series of blood transfusions (Case 20, Alexander, Loman, Lesses, and Green [5]). By quantitative scoring, this patient made a gain of 80 points, rising from —196 to —116. It will be noted that he crossed the middle critical level and subsequently remained above that level except for a brief dip nine months later.

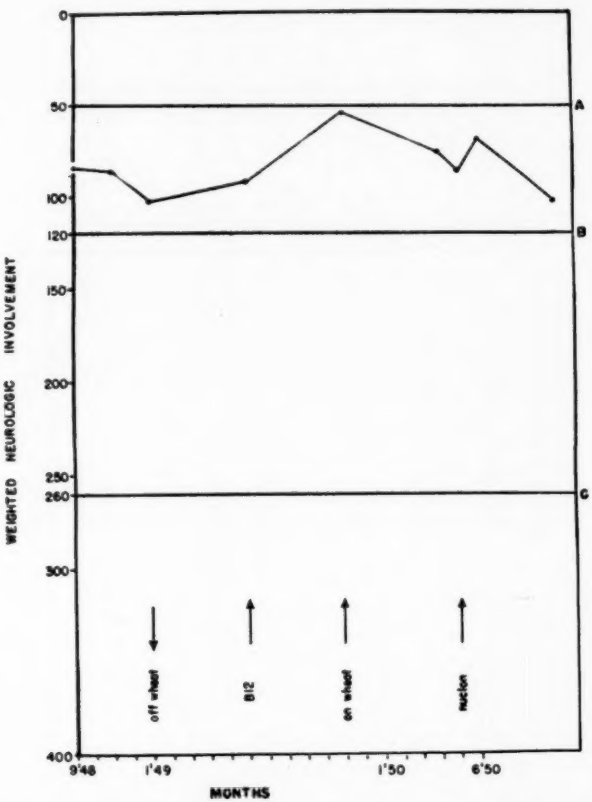

Chart 8.—Graphic representation of course of illness of a woman aged 44, showing insignificant clinical improvement while on a wheat-free diet. Note that the patient at the peak of improvement did not cross the upper critical level (*A*). Duration of illness was three and one-half years at beginning of observation.

In contrast to this patient is another (Chart 6), who achieved clinically insignificant improvement after blood transfusions (Case 34, Alexander, Loman, Lesses, and Green [5]). Although purely quantitative evaluation showed that she gained slightly more than the preceding patient, namely, 83 points, bringing her from —230 to —147, she failed to cross a critical level, and her over-all disability status

remained unchanged. This patient was subsequently treated with testosterone, with similarly insignificant improvement, and finally with corticotrophin, on which she gained 72 points, bringing her up to, but not across, the middle critical level. Thus, all her gains, although representing a considerable increase in score points, remained clinically insignificant.

This general principle of the importance of crossing a critical level was also evident in patients with less severe involvement. Chart 7 is the graph of a woman

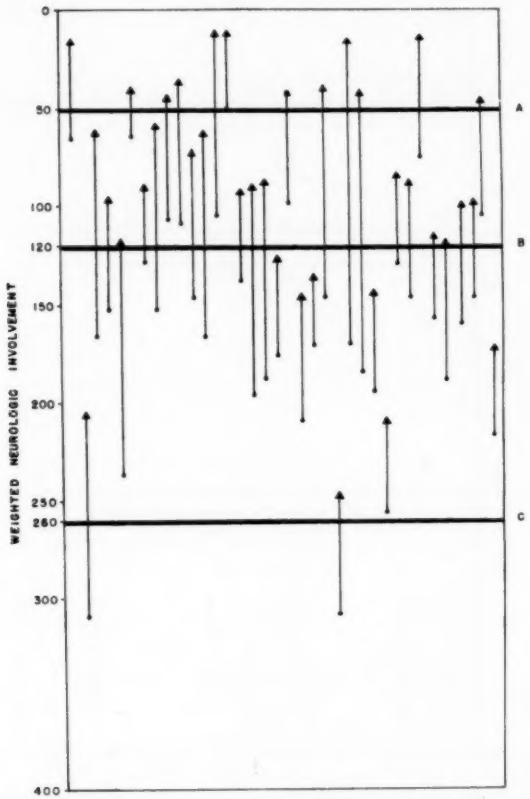

Chart 9.—Graphic representation of 36 instances of clinically significant improvement in 34 of 100 unselected consecutive patients. Note that improvement in most instances extends across critical levels.

whose illness was of two-and-a-half-years' duration and who improved significantly during nine months under observation, gaining 50 points, from —65 to —15, with subsequent maintenance of that level of improvement. Her subjective and obvious improvement in performance coincided with her crossing the upper critical level.

The improvement of this patient is quantitatively comparable to that of another patient who gained 48 points, from —103 to —55, over a 10-mo. period, but whose

improvement was clinically insignificant because it was not associated with improvement in over-all disability status and with subjective improvement. As indicated in Chart 8, this improvement did not carry the patient above the upper critical level. When she became discouraged and abandoned treatment, she again relapsed, without having been aware that she had improved at all, essentially because her gains did not carry her across a critical level.

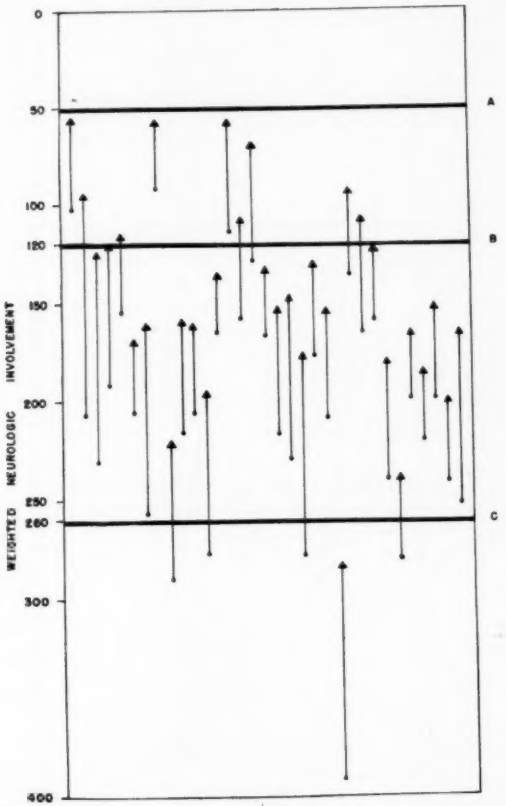

Chart 10.—Graphic representation of 33 instances of clinically insignificant improvement in 27 of 100 unselected consecutive patients. Note that improvement in most instances does not extend across critical levels.

It is apparent in comparing the graphs in Charts 7 and 8 that the slope and extent of improvement in these two cases are very similar indeed, with a gain of 50 points in nine months, versus a gain of 48 points in 10 mo. The outstanding difference is that in the first case the improvement carried the patient across a critical level, whereas in the second case it failed to do so.

The entire body of data of the study were subsequently put to this test of critical level. All instances of clinically significant improvement were plotted on Chart 9,

and all those of clinically insignificant improvement, on Chart 10. In these two graphs the curves have been changed into perpendicular lines, the lower point representing the starting level of the individual patient, the arrow tip indicating the peak of improvement achieved.

In the cases of clinically significant improvement (Chart 9), the amount of improvement, expressed in score points, varied from 27 to 156, the average being 72.

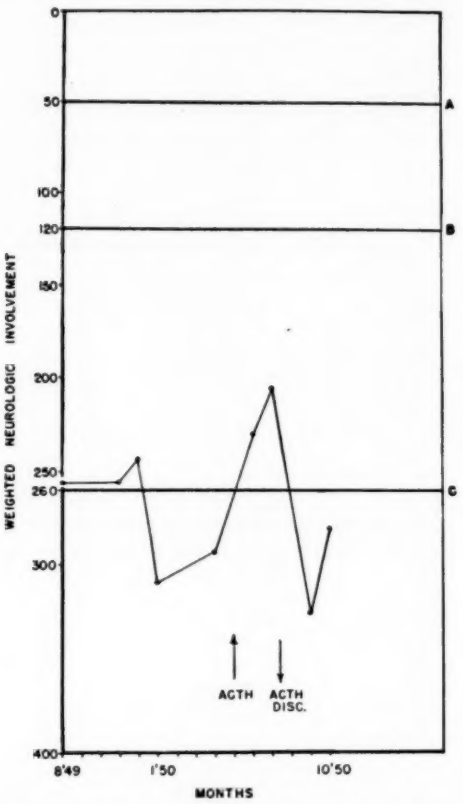

Chart 11.—Graphic representation of effect of corticotrophin on the course of illness of a woman aged 54. The patient received 3.8 gm. of corticotrophin over a period of 59 days. Duration of illness was eight years at beginning of observation.

TABLE 2.—*Data in Relation to Critical Levels Crossed*

	No. Patients	Instances of Improvement	Total Points Gained: Average	Critical Level Crossed		Top or Middle Critical Level Crossed		Top Critical Level Crossed	
				No.	%	No.	%	No.	%
Clinically significant improvement	34	36	72	30	83	28	77	12	33
Clinically insignificant improvement	27	33	60	10	30	6	18	0	0

It is clearly evident that the vast majority of the lines of improvement pass through a critical level. Statistical study (Table 2) showed that a critical level was crossed in 30 instances (83%); the upper or middle critical level was crossed in 28 instances, or 77%, and the upper critical level was crossed in 12 instances, or 33%.

In the cases with clinically insignificant improvement (Chart 10), the number of score points gained is surprisingly similar, varying from 30 to 113 points, with

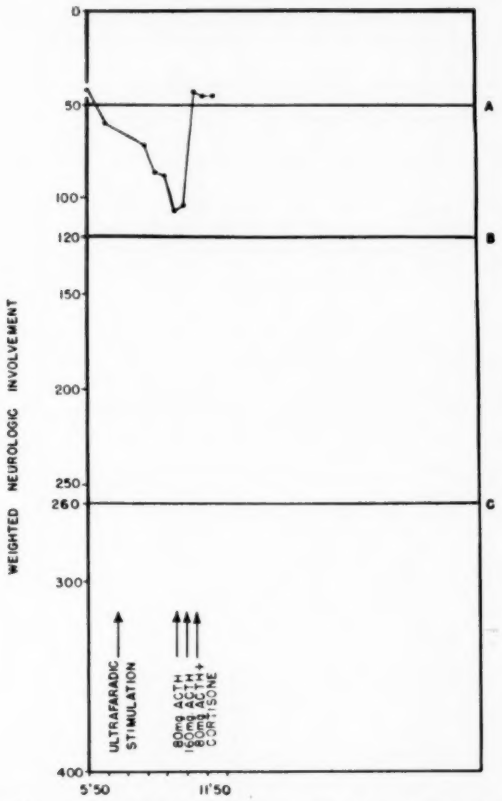

Chart 12.—Graphic representation of effect of corticotrophin and of corticotrophin combined with cortisone on the course of illness of a man aged 21. The patient received 3.5 gm. of corticotrophin over a period of 30 days. Duration of illness was one year at beginning of observation.

the average falling at 60. From the point of view of the location of the starting points of the individual lines, however, it becomes obvious that few could cross a critical level. Of the total group (Table 2), a critical level was crossed in only 10, or 30%; the middle critical level was crossed in only 6 instances (18%), while the upper critical level was crossed in none.

The relation of critical levels to the clinical significance of improvement does much to explain one of the important sources of error in the evaluation of response to therapy in multiple sclerosis—specifically, that slight improvement in neurologic signs and symptoms extending across a critical level may be clinically significant, whereas marked improvement in neurologic signs and symptoms, but limited to areas between critical levels, may be ignored or regarded as insignificant. Quantitative evaluation of the status of the patient at the outset of therapy and after its

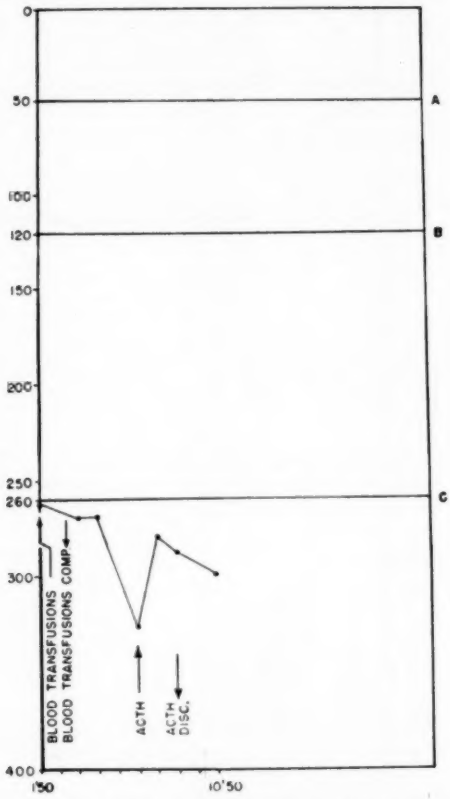

Chart 13.—Graphic representation of effect of corticotrophin on the course of illness of a woman aged 53. The patient received 4.4 gm. of corticotrophin over a period of 66 days. Duration of illness was two years at beginning of observation.

completion will undoubtedly be of great aid in the realistic evaluation of response to therapy.

Thus, the concept of critical steps, made possible by our rating scale, gave us a new understanding of response to therapy in multiple sclerosis. It explains the often puzzling apparent cures expressed in marked improvement of over-all disability status by noting their actual quantitative aspects with reference to critical levels of

neurologic involvement and disability. In a patient who hovers just below a critical level, a relatively slight improvement, easily obtainable by encouragement or other invigorating measures (practically any therapeutic measure may be worth at least 25 points), may push him across a critical level and so give rise to a seemingly unduly marked improvement. This fact obviously explains some of the astonishing cures reported from time to time from various centers of healing, lay and otherwise, especially when these centers of healing cater to a clientele traveling from far distances. The patient who is likely and eager to travel a long distance to be cured is usually the one whose anxiety has been aroused by recently having crossed a critical

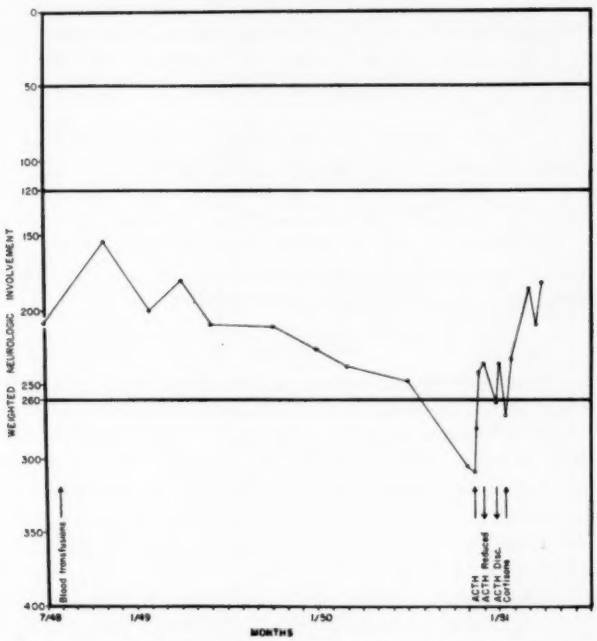

Chart 14.—Graphic representation of the course of illness over two years nine months of a woman aged 27, showing clinically insignificant improvement after blood transfusions in 1948, followed by steady decline throughout most of 1949 and 1950. Clinically significant improvement with corticotrophin therapy, followed by cortisone therapy, began in November, 1950, continuing to the time of this report. The patient received 4.2 gm. of corticotrophin over a period of 57 days. Duration of illness was four years at beginning of observation.

level on the way down. Encouragement may easily help him across that critical level on the way up—alas, only for a short time.

QUANTITATIVE EVALUATION OF THE LIMITS OF SPECIFIC FORMS OF THERAPY: ILLUSTRATIVE CASES

Quantitative evaluation of the patient is likewise helpful in establishing a more realistic view regarding the actual effect of certain forms of therapy, such as recent

trials of corticotrophin (ACTH) and cortisone. In studies carried out in collaboration with Dr. Peter H. Forsham and Dr. George W. Thorn, it was found that the disease may be alleviated temporarily by corticotrophin to the extent of 88 points, that is, roughly by one-fifth the total extent of the illness. The clinical result, however, depends on whether this amount of improvement leads the patient across a critical level. As shown in Chart 6, an improvement of 72 points on corticotrophin therapy remained clinically insignificant because it did not lead to the patient's crossing of a critical level. An improvement of 88 points, the maximum we found in using corticotrophin (Chart 11), was regarded as clinically significant because it led across a critical level and enabled a wheel-chair-bound patient to walk with minimal assistance. She relapsed again after discontinuing the corticotrophin therapy. An improvement of 65 points leading across the upper critical level, obtained by corticotrophin and maintained by cortisone, was likewise clinically significant, the patient's abnormal gait disappearing after he crossed the upper critical level (Chart 12).

For another patient (Chart 13) an improvement of 47 points remained clinically insignificant because it did not lead across a critical level.

At present, we are in the process of exploring the limits of improvement obtainable with cortisone, especially after preparatory treatment with corticotrophin (Chart 14). Quantitative evaluation of the limits of treatment will, I think, aid greatly in preventing unrealistic overevaluation of the amount of improvement obtained during various trial-treatment procedures.

SUMMARY

This paper presents a scoring method for the quantitative evaluation of neurologic involvement and disability based on continuing reexaminations of 212 multiple-sclerosis patients at frequent regular intervals over a three-year period.

The scoring system is based on 50 individual variables derived from the neurologic examination and scored according to the presence or the degree of the abnormality found, allowing a choice of some 100 different scores. The sum of these individual scores, the total examination score, is considered representative of each particular examination, and has been found to correlate well with the over-all clinical status of the patient. Possible total scores range from 0, for a patient with no neurologic abnormalities, to a maximum of —500, for a totally disabled patient. Such a quantitative method permits objective evaluation of the course of the disease in time with or without therapy both in individuals and in groups. Investigation of the relation between changes in score and changes in clinical status revealed the existence of three major critical levels in recovery or decline. It was found that patients whose scores were above the upper critical level (—50) showed no abnormalities of gait; those above the middle critical level (—120) showed various abnormalities of gait but did not require the support of another person while walking, whereas none of those above the lower critical level (—260) were bedridden or confined to a wheel chair.

A longitudinal study of patients with chronic progressive disease revealed a continuing process of gradual attrition, in addition to specific attacks. The crossing of a critical level on a downhill course may sometimes give the impression of an acute exacerbation.

In patients who improved spontaneously or in response to therapy, significant clinical improvement was noted whenever the patient gained sufficient points to pass above one of these critical levels, whereas an equal, or even greater, gain in points by a patient which did not lead him across a critical level brought about no significant clinical improvement. This concept of critical steps has permitted new understanding of therapeutic response in multiple sclerosis by explaining the often puzzling apparent cures expressed in marked improvement of over-all disability status in spite of relatively slight neurologic improvement as resulting from the crossing of a critical level. This method of quantitative evaluation of the amount of improvement obtained in its relationship to the scored quantitative status of the patient prior to treatment and the critical levels of disability is an important aid in the realistic evaluation of the effects and limits of various forms of therapy.

INHERITANCE OF MANIC-DEPRESSIVE PSYCHOSIS

DAVID J. MERRELL, Ph.D.
MINNEAPOLIS

THE ROLE of heredity in the etiology of manic-depressive psychosis has often been investigated, but the results have given rise to a variety of interpretations. A résumé of certain aspects of the knowledge about manic-depressive phychosis may clarify the genetic situation.

The scope of the problem can be outlined to some extent from the annual reports of the Bureau of the Census.[1] The statistics indicate that for at least the past 25 yr. some 12,000 new patients with manic-depressive psychosis have been admitted to institutions for permanent care each year (Table 1), a total of about 300,000 new patients. This rather constant number of annual admissions represents a decrease in the proportion of persons with manic-depressive psychosis among the first admissions with psychosis. There appear to be at least two reasons for this change. The changing age structure of the general population has increased the number of persons living long enough to become subject to senile psychoses or to psychoses with arteriosclerosis. At the same time, there is a tendency to define manic-depressive psychosis more narrowly, so that disorders formerly diagnosed as manic-depressive psychosis now appear to be classified as schizophrenic, or perhaps involutional, psychoses.

Table 2 contains data concerning first admissions, readmissions, and discharge of patients with manic-depressive psychosis from state institutions. The cyclical nature of the psychosis is reflected in the high rate of recovery, discharge, and readmission. The proportion of recoveries among discharged patients is well above that for all psychoses except the involutional and alcoholic forms, but it appears to be declining.

The median age at first admission to state hospitals is significantly higher for males than for females (Table 3). In Slater's[2] material on age of onset there is a similar difference between the sexes. The number of females with manic-depressive psychosis admitted to institutions has always been greater than the number of males with the psychosis (Table 4). There is a definite trend toward an even greater inequality in the sex ratio in recent years. A most interesting aspect of the information presented in the tables is the frequency with which various trends of this sort are found. The proportion of persons with manic-depressive

From the Dight Institute for Human Genetics, University of Minnesota.

1. Patients in Mental Institutions, United States Department of Commerce, Bureau of the Census 1923, 1933-1946.

2. Slater, E.: Zur Erbpathologie des manisch-depressiven Irreseins: Die Eltern und Kinder von Manisch-Depressiven, Ztschr. ges. Neurol. u. Psychiat. **163**:1-47, 1938.

psychosis among first admissions and among readmissions has shown a steady drop. The proportion of women among patients with illnesses diagnosed as manic-depressive psychosis and involutional psychosis has increased regularly (Table 4). These

TABLE 1.—*Diagnosis of First Admissions with Psychosis to Hospitals for the Permanent Care of Psychiatric Patients, for the United States* [1]

Year	Total No. with Psychosis	Manic-Depressive Psychosis		Involutional Psychosis		Schizophrenia	
		Total No.	%	Total No.	%	Total No.	%
1946	120,761	12,078	10.0	6,888	5.7	29,753	24.6
1944	111,325	11,811	10.6	5,239	4.7	29,010	26.1
1942	98,424	11,026	11.2	4,780	4.9	22,643	23.0
1940	90,940	10,433	11.5	4,556	5.0	20,457	22.5
1938	93,541	12,282	13.1	3,845	4.1	21,279	22.7
1936	90,880	12,721	14.0	3,142	3.5	19,818	21.8
1934	82,475	12,079	14.6	2,315	2.8	18,397	22.3
1922	64,656 *	11,393	17.6	1,803	2.8	15,526	24.0

* Alcoholics, drug addicts, epilepties, and mental defectives have been subtracted from the total listed to make it comparable to other totals.

TABLE 2.—*First Admissions, Readmissions, and Discharges from State Institutions* [1]

Year	First Admissions			Readmissions			Discharges		
		Manic-Depressive Psychosis			Manic-Depressive Psychosis			Manic-Depressive Psychosis	
	Total with Psychosis	%	% Female	Total with Psychosis	%	% Female	Total with Psychosis	%	% Recovered
1946	77,518	9.0	64.8	.....	....	....	54,170	19.9	45.0
1944	74,958	9.6	63.9	21,421	25.3	64.9	52,821	19.6	50.7
1942	75,647	10.1	60.7	21,263	26.1	60.9	52,877	20.1	51.6
1940	69,511	10.5	58.6	20,285	26.3	62.3	46,700	22.1	54.4
1938	69,753	12.4	58.9	18,625	28.2	61.3	45,841	23.6	56.1
1936	68,257	13.3	57.5	16,649	29.3	60.3	39,570	24.9	56.8
1934	63,006	13.9	56.9	15,822	29.9	58.9	38,126	26.1	56.3
1932	61,178	15.7	54.2	15,074	30.6	57.4	34,495	27.1	....

TABLE 3.—*Median Age of First Admission for Manic-Depressive Psychosis to State Hospitals* [1]

Year	Median Age		
	Total	Males	Females
1946	40.1	43.1	38.6
1945	39.0	41.5	37.8
1944	38.9	41.1	37.8
1943	39.3	40.9	38.4
1942	39.0	40.2	38.3

trends, and others, are statistically highly significant, but it is probable that few have biological significance.

Two interesting parallels between involutional psychosis and manic-depressive psychosis should be noted. The first is the parallel shift in the sex ratios toward a higher proportion of females. The second is the similar high rates of recovery. The increase in the total number of patients with involutional psychosis may represent a shift in emphasis favoring this diagnosis in older patients. The statement in Sadler's [3] "Modern Psychiatry" that "diagnosis . . . is usually not difficult,

3. Sadler, W. S.: Modern Psychiatry, St. Louis, C. V. Mosby Company, 1945.

especially in patients above thirty to thirty-five years of age whose history discloses two or more previous attacks" suggests that an initial diagnosis of manic-depressive psychosis is considerably less reliable than later diagnoses. Slater [2] emphasized this point and selected for study only patients who had had at least a clear manic and a clear depressive attack or three manic or three depressive attacks, all separate and all ending in complete recovery. Such a procedure considerably reduces the chances of error due to faulty diagnosis. Fundamentally, the validity of a genetic study depends on the precision with which the affected groups can be separated and the assurance with which the entity under study can be distinguished from other, similar conditions. At present, it is clear that a major problem in any genetic study of manic-depressive psychosis is the establishment of adequate diagnostic criteria.

RESULTS OF GENETIC STUDIES

In the study of the inheritance of a particular human trait, the evidence may be of several kinds. The most reliable data ordinarily come from twins but, unfortunately, give little knowledge as to the mode of inheritance. Differences in the

TABLE 4.—*Percentage of Females Among First Admissions to State Institutions* [1]

Year	Manic-Depressive Psychosis	Involutional Psychosis
1946	64.8	77.1
1944	63.9	78.3
1942	60.7	78.8
1940	58.6	74.6
1938	58.9	75.1
1936	57.5	75.0
1934	56.9	69.1
1932	54.2	61.8

frequency of a trait in different populations and a high incidence of the trait among the relatives of an affected person both indicate a genetic basis. Family pedigrees offer the best source of information as to the mode of inheritance of a character, but such factors as small family size and different modes of inheritance for similar traits often obscure the results.

The data on twins (Table 5) are drawn from the work of Kallmann [4] and Rosanoff, Handy, and Plesset [5] with unselected series of cases. Luxenburger's data are cited by Rosanoff and associates, but only that portion obtained from an uninterrupted series is included here. The large number of cases Luxenburger obtained from the literature have far too great a proportion of identical twins to form a very reliable sample. In agreement with the data in Table 4, 71.8% of 117 manic-depressive twins, both monozygotic and dizygotic, were women (Rosanoff's data [5] only).

The concordance in identical twins is considerably higher than in fraternal twins. Since the environment is generally assumed to be essentially the same for

4. Kallmann, F. J.: The Genetics of Psychoses: An Analysis of 1,232 Twin Index Families, Congrès international de psychiatrie, Paris, 1950.

5. Rosanoff, A. J.; Handy, L. M., and Plesset, I. R.: The Etiology of Manic-Depressive Syndromes with Special Reference to Their Occurrence in Twins, Am. J. Psychiat. **91**:725-762, 1935.

the two types, this large difference must be due primarily to heredity. (Stern [6] gives a very reasonable, lucid discussion of the validity of the twin method.) Since the members of each pair of identical twins have the same genotype, the fact that concordance is not complete indicates that the environment does play a role in the development of the psychosis. Furthermore, not all persons with potential manic-depressive psychosis are destined to become psychotic. This fact is significant in the search for means of controlling the psychosis.

Further evidence for the role of heredity is the greater incidence of manic-depressive psychosis among the relatives of a manic-depressive patient. Slater [2] calculated the frequency of the psychosis in the general population as roughly 0.4±%. This figure agrees well with a number of other estimates cited by Lange.[7] Among the parents, sibs, and children of a manic-depressive patient Slater estimates the frequency to be 30 to 60 times as great (12 to 24%).

TABLE 5.—*Incidence of Manic-Depressive Psychosis Among Relatives of Patients with Manic-Depressive Psychosis*

	Twins			
	Monozygotic		Dizygotic	
Investigator	No.	% Concordant	No.	% Concordant
Rosanoff and others [5]	23	69.6 *	67	16.4 *
Luxenburger † (uninterrupted series)	4	75.0 *	13	0.0 *
Kallmann [4]	23	95.7 *	52	26.3

	Sibs		Parents		Children	
Investigator	No.	% Affected	No.	% Affected	No.	% Affected
Kallmann [4]	184	23.0	122	23.4	...	...
Banse ‡	292	9.0 (18.0) §	160	3.4 (10.3)	...	...
Röll, A., and Entres, J. L.: Ztschr. ges. Neurol. u. Psychiat. **156**: 169-202, 1936	225	9.5 (10.7)	166 ‡	10.4 (13.0)	132 ‡	9.7 (10.9)
Slater [2]	...	...	504	10.2 (15.5)	491	12.8 (15.2)
Hoffman ‡	...	...	...	...	139	13.8 (21.2)

* Unadjusted percentage; all others adjusted by Weinberg method.
† Cited by Rosanoff and others.[5]
‡ From Lange,[7] after Schulz.
§ Figures in parentheses include doubtful cases.

Since human populations differ from one another fundamentally in the frequency of various genes, the frequency of hereditary traits may be expected to vary in these different groups. A review by Schottky [8] summarized the results of such studies, which indicate that differences in frequency of the psychosis do exist in different populations and in different areas. For example, the frequency of the psychosis appears to be greater in southern than in northern Germany. Furthermore, a higher incidence of manic-depressive psychosis in Jews than in the people among whom they live has been generally found. These, and similar, results,

6. Stern, C.: Principles of Human Genetics, San Francisco, W. H. Freeman and Co., 1949, chap. 23.

7. Lange, J.: Das zirkuläre Irresein, in Just, G.: Handbuch der Erbbiologie des Menschen, Berlin, Julius Springer, 1939, Vol. 5, pp. 873-932.

8. Schottky, J., and others, editors: Rasse und Krankheit, München, J. F. Lehmanns Verlag, 1937.

fragmentary and inconclusive alone, nevertheless support a hereditary basis for the psychosis.

Since the data on twins indicate a certain discordance, it is possible that some other manifestation may reflect the manic-depressive tendency. The correlation of suicide with manic-depressive psychosis in families indicates that suicide is an alternative expression of the genotype.[9] The suicidal tendency of many patients with manic-depressive psychosis is marked, so that this correlation is not surprising. In many cases the suicide is evidently the first patent symptom of the psychosis. Of 318 deaths listed by Slater,[2] including those of probands, their parents, and their children over 20 yr. of age, 6.6% were due to suicide, or about seven times the average rate.

Finally, the incidence of the psychosis among the relatives of persons with manic-depressive psychosis must be considered in order to discuss the mode of inheritance. The critical matter of diagnosis, again, is the chief stumbling block. The contradictions and wide discrepancies in the reported results are due oftenest to differences in the investigators' interpretations of the range of types to be included in the probands and in their affected relatives. Hoffman, for example, using the broadest interpretation of the affected group, found 60.0% affected persons among children one of whose parents had a manic-depressive psychosis. Calculated by Schulz on the diagnostic basis used by most other authors, this figure became 13.8%, or 21.2% when persons with questionable manic-depressive psychosis were included (Lange[7]). A further difficulty in the determination of the proportion of affected relatives lies in the fact that the psychosis is not manifest at birth, as is a simple genetic trait, such as albinism. Therefore, corrections must be applied to the data to allow for the possibility that the psychosis may still develop in some of the unaffected relatives. The most widely used correction is the "short method" devised by Weinberg. This method eliminates all persons under 20 as having had no chance to become manic-depressive; of those between 20 and 50, one-half the persons with potential manic-depressive psychosis are assumed to have become psychotic; it is assumed that all cases of manic-depressive psychosis have developed among the persons over 50.

Table 5 gives a selection of the data from various authors calculated by the Weinberg method for parents, sibs, and children of patients with manic-depressive psychosis. Two points should be noted at once: (1) the much higher incidence of the psychosis among these relatives than in the general population, and (2) the rough equality of the frequency of the psychosis among these groups. The actual frequency at this point is relatively unimportant. As has been pointed out, these figures will vary to a considerable extent, according to the method of evaluation of the data and the corrections made. However, when estimated on a roughly comparable basis, the incidence turns out to be about the same in all three groups. This fact is of particular significance. It should be noted that the concordance in fraternal twins, actually another estimate, genetically, of the frequency among sibs, corresponds fairly well with the data on sibs.

If a trait of this frequency were due to a single recessive gene, the incidence of the trait would be much lower in the parents and children than among the sibs

9. Merrell, D. J.: Unpublished data.

of persons with manic-depressive psychosis. This fact may be illustrated by means of the Hardy-Weinberg formula

$$p^2 + 2pq + q^2 = 1$$

$p^2 = 0.004$ = frequency of persons with manic-depressive psychosis (Slater [2])
$2pq = 0.118$ = frequency of heterozygotes
$q^2 = 0.878$ = frequency of homozygous normal persons
$p = 0.063$ = frequency of the postulated recessive gene for manic-depressive psychosis
$q = 0.937$ = frequency of the normal allele

With these terms, the expected proportions of persons with manic-depressive psychosis among the parents, sibs, and children of patients with the psychosis may be calculated as follows:

Proportion of parents with manic-depressive psychosis

$$\frac{\frac{1}{2}p^2(2pq) + (p^2)^2}{(2pq)^2 + p^2(2pq) + (p^2)^2} = \frac{p}{4q^2 + 2pq + p^2} = 0.017, \text{ or } 1.7\%$$

Proportion of sibs with manic-depressive psychosis

$$\frac{\frac{1}{4}(2pq)^2 + \frac{1}{2}(2pq)(p^2)^2 + (p^2)^2}{(2pq)^2 + p^2(2pq) + (p^2)^2} = \frac{q + p^2}{4q^2 + 2pq + p^2} = 0.259, \text{ or } 25.9\%$$

Proportion of children with manic-depressive psychosis

$$\frac{\frac{1}{2}p^2(2pq) + (p^2)^2}{p^2q^2 + p^2(2pq) + (p^2)^2} = p = 0.063, \text{ or } 6.3\%$$

Although these calculations are based on some simplification of the problems involved, the calculated results differ so greatly from the results obtained that the possibility that the psychosis is due to a single recessive can be eliminated. Since a sex-linked recessive would result in a preponderance of affected males, that possibility can also be eliminated.

A theory which has been suggested to account for the excess of affected female patients is sex-linked dominance. Slater [2] has shown the improbability of this theory. Male propositi would be expected to show primarily affected mothers and affected daughters, but Slater's data, though scant, show no evidence of such a distribution. There are several suggestions that the excess of affected females is more apparent than real. The excess of women among institutionalized patients was not paralleled among those seen in private practice (Paskind [10]). Weinberg [11] and others have suggested that the higher frequency of suicide among men may account for the difference. However, even though there may be a real difference between the proportion of affected females and that of affected males, that difference alone is not conclusive evidence of sex-linked dominance. The evidence to the contrary is sufficient to leave a reasonable doubt as to its validity.

The only remaining possibility among theories involving only a single gene is an autosomal dominant. A variety of additional theories involving two or more genes, sex-linked or autosomal, or combinations of the two types, have been sug-

10. Paskind, H. A.: Manic-Depressive Psychosis as Seen in Private Practice: Sex Distribution and Age of Incidence of First Attacks, Arch. Neurol. & Psychiat. **23**:152-158 (Jan.) 1930.

11. Weinberg, W.: Zur Vererbung bei manisch-depressivem Irresein, Ztschr. ang. Anat. **6**:380-388, 1920.

gested (review by Lange[7]). These more complex theories have usually been formulated to furnish an exact Mendelian explanation for a group of data. Since the precision of these theories exceeds the accuracy of the data they are designed to fit, their value is questionable. In fact, they are so cumbersome that their usefulness, in the present state of knowledge, is quite limited. The critical test of any theory at present appears to be whether it would cause an equal frequency of the psychosis in the parents, sibs, and children of persons with the manic-depressive psychosis. Since none of the simpler multiple-gene theories seem able to stand this test, more or less by the process of elimination, the only theory left is that of a single autosomal dominant gene.

For an autosomal dominant, about 50% of the parents, sibs, and children would be expected to show the trait. In Table 5 the figures ranged from 10 to 25% for each of the three groups. This consistency is itself evidence for dominance. The deviation from the expected percentage should not be surprising. In genetic terms, a gene which is not always expressed is said to show incomplete penetrance. Since it has already been shown that in identical twins with the same genotype and similar environments there is some discordance, incomplete penetrance has already been demonstrated. The earlier age of onset and the higher frequency in women can also be regarded as evidence for differences in penetrance between the sexes, rather than for sex-linked dominance. Since the great majority of affected persons, on the assumption of a dominant, are heterozygous and carry also the normal allele, the variability in expression may be expected on these grounds as well. Finally, the affected persons have generally been defined as institutionalized patients. Campbell[12] has recently emphasized the prevalence of mild cases of manic-depressive psychosis. The use of institutionalization as a criterion is, therefore, a very conservative method of determining the frequency of the trait.

Therefore, at present, the simplest theory of the mode of inheritance of manic-depressive psychosis which is consistent with the data is that of a single autosomal dominant gene with incomplete penetrance.

COMMENT

It may be worth while to dwell briefly on some of the implications of the data. The problem of defining the affected groups stands out as the major one to be solved before further progress in genetic studies is possible. The evidence that heredity plays a role in the etiology of the psychosis is unmistakable. This fact should be useful in attacking the problem of diagnosis. Since inherited traits with morphological, physiological, or biochemical manifestations have their physical origins in the chromosomes, physically measurable differences should exist between the normal and the abnormal, or potentially abnormal, persons. Therefore, psychiatric examinations should be supplemented by additional physical and chemical tests. (As an interesting side light on the question of the physical basis of the psychosis, the success of shock therapy, a rather drastic physical treatment, should be noted.) The hereditary findings, of course, suggest that the close relatives of persons with manic-depressive psychosis should be most carefully examined because among them the highest proportion of potential cases of the psychosis will

12. Campbell, J. D.: Mild Manic-Depressive Psychosis, Depressive Type: Psychiatric and Clinical Significance, J. Nerv. & Ment. Dis. **112**:206-236, 1950.

be found. Examination of the sibs of persons with manic-depressive psychosis, for example, should furnish considerable information on the prepsychotic condition if proper tests can be devised. Efforts in this direction thus far have not been notably successful, but these failures, of course, are not conclusive evidence that such differences between normal and abnormal do not exist. As yet studies of personality, body type, biochemistry, etc., have been of no great help in actually picking out persons who later become manic-depressive.

Experimental work on vertebrate behavior indicates that it is the resultant of the interplay between the environment and the nervous and endocrine systems of the organism. Such a simple environmental change as increasing length of day may cause a series of pronounced physiological and behavioral changes. While the situation in man is undoubtedly more complex and less rigid, there is no reason to believe that similar relationships do not exist. The very complexity of these interrelationships is probably largely responsible for the difficulty in classifying the various neurotic and psychotic conditions into just a few categories. It is probable that the genetic factors associated with manic-depressive psychosis in some way influence the normal function of the nervous system or the endocrine system. Furthermore, the fact that conditions very similar to this psychosis seem to have a clear psychogenesis need not be surprising. It is quite conceivable that a strong enough external disturbance could cause a somatic upset similar to the genetically conditioned one. In other words, the breakdown may be thought of in terms of threshold. In normal persons the threshold is high, but may still be reached under unusual stress. In persons carrying the genetic factors for the psychosis, the threshold is considerably lower but will not be exceeded in all cases.

SUMMARY

1. The diagnosis of manic-depressive psychosis is shown statistically to be less common than formerly, and the definition of the psychosis can be assumed to be less inclusive than before.

2. Figures on discharges and readmissions confirm the cyclical nature of the psychosis.

3. Evidence that women are more severely affected than men is to be found in the earlier age of onset and of first admission and in the greater proportion of affected women.

4. Data on twins show conclusively that heredity is involved in the etiology of the psychosis.

5. The high incidence of the manic-depressive psychosis among the relatives of persons with this psychosis and the difference in frequency of the psychosis in different populations are further evidence for the role of heredity.

6. The frequency of the psychosis is about the same among the parents, sibs, fraternal twins, and children of patients with manic-depressive psychosis. The best genetic explanation for the data is that of a single autosomal dominant gene with incomplete penetrance.

PSYCHOANALYSIS AND DYNAMIC PSYCHIATRY

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I

IT IS THE purpose of this paper to discuss the relationship of psychoanalysis to dynamic psychiatry, to demonstrate the derivation of the latter from the former, and to point out their significant differences.

A dynamism is a power or quality which produces action. It operates through a transfer of energy. Any theory which is based on the operation of forces or shifts of energy is a dynamic theory. Psychoanalysis is such a theory, but it is not the only such theory. Contrary to common opinion, there were psychodynamic theories of personality antecedent to psychoanalysis; and there are psychodynamic theories of personality today which are not psychoanalytic.

Primitive man looked upon all illness as "mental," that is, spiritual. The forces (energies) of nature which he was consciously affected by, whether it be as regards the condition of his life or the state of his body or mind, were anthropomorphized as spirit forces which acted upon him and within him.

The ancient Hindus considered human life in all its forms "as a series of links in a long chain of natural functions." The various mental states—waking, sleeping, dreaming, stupor, or ecstasy—were considered to be manifestations of the partnership of the soul and its physical instrument, the body—force or energy acting through or upon structure.[1]

Hippocrates, while clinically eclectic, "was inclined to consider that purely psychological forces preside over all our organic functions, including those of the brain. He thought in terms of a *vital force*—something akin to Bergson's *élan vital* —a force bound in some way to the body through the sensory and motor systems, but capable of acting on its own initiative through the agency of the body." [1] His medical psychology represented a serious attempt to bring together whatever the knowledge of his day had put at his disposal in order to construct a unitary system of man as a whole, rather than man as a conglomerate of separate units.[1]

However, it was the Greeks who established the tradition of considering the human mind as the exclusive province of philosophy. Until the time of Braid, Liebeault, and Charcot, it was not the doctors, but the philosophers, who pondered the problems of the mind in the body. The German psychiatrists of the first half of

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From the Institute for Psychosomatic and Psychiatric Research and Training, Michael Reese Hospital.

1. Zilboorg, G.: A History of Medical Psychology, New York, W. W. Norton and Company, 1941.

the 19th century who concerned themselves with the subjective state of the mentally ill were contemptuously discarded by their colleagues as "philosophers" and "theologians." In contrast, the historical significance of the Charcot school lies in the fact that it succeeded in capturing the neuroses for psychiatry and for medicine. From these sources developed a new orientation which began to take into consideration the real life of man in his social setting and with his problems as a human being.

This development did not follow a very direct line. The interest of 19th century French psychiatry remained preponderantly in the description, separation, and analysis of mental phenomena and their aberrations. Even Janet, despite his adherence to what he called psychological methods, cannot be considered to have held a dynamic point of view. His basic theory of constitutional degeneration removes him from the class of those who looked upon psychic phenomena as evolving energic phenomena. Bernheim was groping much closer to the truth when he spoke of the therapy of hysteria as "not suggestion but de-suggestion." His therapy was directed toward the removal of the noxious ideas which underlay the symptoms for which they were held to be responsible; that is, the pathogenic mental content was "de-suggested," and psychic energy was thus channeled away from the symptom which it sustained.[1] In the end, it remained for Freud, under the impetus of Charcot and Bernheim, to develop a system of psychotherapy which was fully dependent on the conception that psychic phenomena are produced by specific forces operating in a specific manner and direction.

In 1893 Freud and Breuer published their epochal paper on the mechanisms of hysterical phenomena.[2] The discovery that unconscious memories and fantasies could emerge with relevant affect under hypnosis and that this "catharsis" could be therapeutically effective was, in fact, the discovery of the unconscious and the demonstration of its dynamic quality. A procedure which had produced an energic change, manifested by remembrance and abreaction, had at the same time discovered the cause and effected the cure. The era of dynamic psychiatry was born.

II

The word "psychoanalysis" is in itself only a description of the procedure which Freud ultimately evolved for studying the psyche and for treating its ills. However, in addition to referring to a technique of therapy and investigation, it has come also to designate the body of knowledge acquired by the use of the technique and the scientific hypotheses which have been derived from this knowledge. These hypotheses may be grouped as follows: the genetic, the structural, and the dynamic theories of the personality. Inclusive of all of these is the general principle of determinism, a principle which is basic to all science and which may be stated as follows: The immanent present is the resultant of the convergence of forces emanating from the remote, the recent, and the immediate past. Knight has applied this principle to psychoanalysis and psychiatry in his statement:[3]

> The individual's total make-up and probable reactions at any given moment are strictly determined by all the forces, early and late, external and internal, past and present, which have played on him and are playing on him.

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2. Breuer, J., and Freud, S.: Studies in Hysteria, Nervous and Mental Disease Publishing Company, 1936.

3. Knight, R. P.: Determinism, "Freedom," and Psychotherapy, Psychiatry **9**:251, 1946.

It is this basic assumption of psychogenesis which characterizes any psychiatric system which can be called dynamic. In contrast, this assumption is absent from the static concepts of Kraepelin's descriptive psychiatry, the mechanistic theories of the German organicists, and the psychophysical parallelism of William James and Wundt.

Dynamic psychiatry did not come to America with Freud. It had an independent origin here during the last decade of the 19th century, when Adolf Meyer, under the influence of Hughlings Jackson's thinking on the interaction of mind and brain, began the development of his psychobiological theory. Thus, the ground was already fertile for the reception of psychoanalysis. In 1906, Meyer wrote:

> Freud has opened the eyes of the physician to an extension of human biology which differs very favorably from the sensational curiosity shop of the literature on perversions.[4]

As early as 1908, while he was the director of the New York State Pathological Institute, Meyer was insisting that cases of so-called functional mental illness be worked up on the basis of Freud's theories and an attempt made at their psychoanalytic formulation.[4]

Psychobiology is interested in the personality as a whole. It assumes that "matter and its functions belong inseparably together, forming a unit, functioning as a unit." This is known as the "principle of integration" and is based on the concept of a hierarchy of levels of integration: anatomic, physiologic, neurologic, and psychobiologic. The last is "formed by the mentally integrated functions, does not exist in the abstract, and necessarily includes the lower levels." Thus, a reflex arc is not a psychobiological unit; it is a neurophysiological unit. But when it functions as a part of the whole living organism and is the resultant of memories, anticipations, and intentions, then it is psychically integrated and an expression of the personality.

> The most essential characteristic of this psychobiologic personality is that it makes use—with the aid of symbols—of reality and imagination, past, present and future, personal and general, as if everything were here right now and with only this subject.[5]

In other words, Diethelm, whom I have just quoted, is describing, in the terms of the psychobiologic school, the principle of psychic determinism.

But with all of Adolf Meyer's open-mindedness toward psychoanalysis, psychobiology never accepted the theory of the unconscious. Despite the fact that the psychobiological approach necessitates the study of both the overt and the implicit performances of a person, that it considers overt behavior to be "integrated" by implicit inner activity, and that the latter can be "deduced" from the former, Diethelm asserts: "We do not deal with unconscious thinking but with mental functions of which the subject is not aware because of his attention being directed elsewhere." [5]

This brings us to the more immediate consideration of the topic of this paper. American psychiatry has until relatively recently been the psychobiology of Adolf Meyer. In terms of the general concepts of energy and of determinism which I have described, it was operationally dynamic. Still, it has presented us with the paradoxical fact that it failed to evolve a theory which would enable it to develop beyond simple pragmatism. It failed to develop a unifying hypothesis which could account for the "essential quality of meaning or sense and direction which becomes clear

4. Oberndorf, C. P.: Dr. Adolf Meyer (1866-1950) (Obituary), Internat. J. Psycho-Analysis **32**:56, 1951.

5. Diethelm, O.: Treatment in Psychiatry, New York, The Macmillan Company, 1936.

when [psychological phenomena] are viewed in the light of the personal biographical record."[6] American psychiatry has become "dynamic psychiatry," as we know it today, through a synthesis of the psychobiology of Adolf Meyer and the psychoanalysis of Sigmund Freud.

III

The term "dynamic psychiatry" is an indigenous American expression. It is, in a way, a neologism, compounded from the comprehensive term "psychiatry," which literally means "treatment of the mind," and the special term "psychodynamic," which is derived from psychoanalysis and refers to the energy which is manifested in the operations of the psyche. Taken as a whole, it is an idiomatic expression meaning treatment of the mind on the basis of the management of the forces of the mind. It is concerned with the whole man, in his genetic, somatic, behavioral, interpersonal, and social aspects, as seen from the viewpoint of psychoanalysis.

Dynamic psychiatry is the logical outcome of the history of psychiatry in America. Psychobiology had effectively undermined the influence of Kraepelin and the concept of disease entities. Characteristic American optimism had refused to come under the sway of fatalistic German organicism. The individualization of the patient discovered meaning and purpose in the various reaction patterns which we call mental disease. Formulation began to undermine classification. Therapy began to be directed toward the problems of the patient rather than toward his disease. As early as 1909, when Healy began his pioneer work with children, American psychiatry was sufficiently sensitized to the genetic factors in mental illness to see sense in attempting to deal preventively with the problem. As early as 1911, when the New York Psychoanalytic Society was organized, Adolf Meyer and George Kirby were among its charter members. From that time on there has been a steady increase in the influence which psychoanalysis has exerted on the outlook and practice of American psychiatry. European psychiatry has not matched this trend to this day. Indeed, so complete is the rapprochement of psychiatry and psychoanalysis today (particularly as regards psychotherapy) that there has been increasing confusion, not only among lay people but also among psychiatrists and psychoanalysts, as to where the boundary between dynamic psychiatry and psychoanalysis proper is to be found. And yet there is a boundary, and it shall be my attempt now to establish it.

Let us again consider what psychoanalysis is. First of all, it is a method of psychological investigation based on free association. The fundamental premise of the method is that there is an unconscious. The unconscious is the reservoir of the simplest and most primitive of biologically determined forces. These forces are controlled by counterforces, known as defenses. Under the influence of a technical interpersonal situation, known as "analysis," the free associations of the subject are encouraged to emerge. To some extent this tends to occur spontaneously under the "pressure of the unconscious." To a larger extent, a phenomenon known as "resistance" interferes, but can be technically overcome. The free associations consist of the deeply private feelings, impulses, attitudes, and fantasies of the subject. As such, they are only the verbal manifestations of the forces of the unconscious and of the defenses. The psychic energy itself and its distribution and action are

6. Muncie, W.: Psychobiology and Psychiatry, St. Louis, C. V. Mosby Company, 1939.

inferred from what is observed in the analytic situation, even as the physicist deduces the forces within the atom from the phenomena he observes in the cloud chamber. Psychoanalysis is the most important instrument we have for obtaining the kind of data which enable us to deduce the operations of psychic energy.

Secondly, this method of investigation has resulted in the discovery of a large number of facts on the basis of which a body of theory has been elaborated. Some of this is tentative or controversial, but much of it is fully tenable and operationally established. It is not within the scope of this paper to discuss this in detail.

Lastly, it has been demonstrated that the systematic application of the method, according to the technical criteria that have been developed, will, in favorable cases, effect a reorganization of the psychic forces just described, such that there is not simply a symptomatic clinical remission, but actual personality reorganization.

There is no longer any significant doubt about the psychological facts which psychoanalysis has uncovered. The role of early childhood and the family relations; the place of sexuality and aggression; the operation of the various mental mechanisms; the phenomonology of conflict, anxiety, and guilt; the somatic language of the emotions—these are some of the broad categories of psychoanalytic facts that have become an accepted part of the content of psychiatric thought. The existence and meaning of the transference; the operation of repression and resistance; the significance of dreams, of verbalization and catharsis, of dependence and regression are examples of the facts that have passed from psychoanalysis into clinical psychiatry. All of these are usefully applicable outside of analysis. They have enriched our understanding of psychiatric material proper and of human relationships and behavior in general. They have sharpened the possibilities of psychotherapy, making it more rational, more goal-directed. They have enabled the psychiatrist to exercise his therapeutic functions, not blindly motivated by his humaneness, but guided by a principle which enables him to choose a course of action.

Such psychotherapy needs no qualifications, such as "psychoanalytic" psychotherapy, or "analytically oriented" psychotherapy, or "dynamic" psychotherapy. Such qualifications are no more meaningful than would be the description of what a modern medical man does by some such phrase as "pathophysiologically-oriented therapeutics." Rational psychotherapy is based on everything we know today about psychopathology and psychodynamics. It is dynamic psychotherapy because it works with a knowledge of the forces of the mind and with respect to these forces. From this standpoint we can look upon psychoanalysis as the pathophysiology of the psyche. And we can take it for granted that good psychotherapy, whether it is by interview, hypnosis, narcosynthesis, or whatever, is based on this as a foundation.

We see, then, that the chief contribution of psychoanalysis to American psychiatry has been to complete the structure which was originally given it by psychobiology. Without the concept of the unconscious and the things which follow from that concept, the "sense and meaning" which Adolf Meyer observed in mental illness remained without system and unity. With this concept psychiatry really has become holistic.

IV

Thus far I have only made a further contribution to the problem of the place of psychoanalysis in our psychiatric system. But psychoanalysis has two other important aspects: first, as a special technique of psychological research, and, second, as a special method of therapy. I shall consider these in turn.

It has become a cliché to refer to psychoanalysis as a psychological microscope. The analytic situation itself is a rigorously controlled experiment in human relationship, oriented toward the exclusion of the many variables which obscure the quality and meaning of ordinary relationships. When the technique is correctly applied, the events observed are relatively free from artifacts introduced by the activity of the observer. In this setting the phenomenon known as the transference neurosis develops. This is not created by the analyst. It appears under the pressure of the tendency of past attitudes and impulses to repeat themselves. It is permitted to establish itself and to evolve in its own terms and toward its own particular denouément. In the relationship to the analyst there thus recur the significant emotional events of infancy and early childhood. These events do not present themselves as discrete transference episodes, but are part of a continuous process of recapitulation in the present of the continuous past, in the form of affects, fantasies, dreams, impulses, and somatic sets and tensions. It is this restoration of the past in the present that constitutes the microscopic field of psychoanalysis. In this field there reappears the flux of creative and destructive forces which have determined the destiny of the person.

The categories of facts observed and reported by those who have employed the psychoanalytic instrument have already been passingly alluded to. Their detailed presentation is neither possible nor necessary at this time. However, much remains to be discovered in the field of ego psychology, in psychosomatic illness, in nosology, and in the psychoses. To know something psychoanalytically about these means to know it genetically in terms of all the various shifts of psychic energy which have eventuated in the phenomena observed. This will be possible only under the conditions which I have described.

In psychoanalysis the method of therapy is identical with the technique of research. As a therapy, psychoanalysis postulates that the essential factors are the occurrence, the reduction, and the final resolution of the transference. As the means to this end, the analytic procedure involves a systematic interpretive attack on the resistances for the purpose of obtaining explicit verbalization of all thoughts, fantasies, feeling, attitudes, and impulses. To the extent to which this is successful, the patient reexperiences his past in the present; that is, he experiences the transference neurosis with the analyst as its focus. As this evolves, it, too, is subject to systematic interpretation in terms of its connections with the discovered past and the observable present. In the end, the past and present, the once-repressed and the always-remembered, are integrated into the unity of the person.

One of the as yet unsolved problems of psychoanalysis is concerned with the essential nature of psychoanalytic cure. It is not insight; it is not the recall of infantile memories; it is not catharsis or abreaction; it is not the relationship to the analyst. Still, it is all of these in some synthesis which it has not yet been possible to formulate explicitly. Somehow, in a successful analysis the patient matures as a total personality. Somehow, a developmental process which has been halted or sidetracked, resumes its course. It is as though the person, reexperiencing his past in the transference, finds in the new conditions a second chance and "redevelops" while he is reliving.

Without overlooking the fact that as a therapeutic instrument psychoanalysis has a significant number of failures to record, one must also remember that it can and does produce an inner unification of the personality, which in some instances is overtly evident as what we call "character change."

Modern psychotherapy is deeply rooted in the facts and theories of psychoanalysis. It has become a significant part of American psychiatry, particularly during the last 20 years. It deserves its position in psychiatry because it is in a real sense the psychiatrist's reason for being. More than that, however, it justifies itself by having become a truly effective instrument. Nothing which I have to say about it should give the impression that I depreciate its validity and its usefulness. Nevertheless, it is not psychoanalysis even when it is psychoanalytic. This can be stated despite the fact that it sees the problems of the personality as psychoanalysis has revealed them; that it is aware of, and sometimes deals with, transference phenomena and with resistances; that it strives for verbalization and affective expression and insight; that it often cures symptoms dramatically, and sometimes produces long-lasting, beneficial effects. The differences between psychoanalysis and the most extensive psychotherapy are to be found in the difference in technique and in the goal which is striven for and attainable.

Let us approach the problem by way of a paradox; it is much easier to see and to understand specifically why patients get well under psychotherapy than in analysis. Here are some commonly observed examples:

A patient, following the establishment of a good relationship wtih the therapist, begins to verbalize, encounters a topic which bears too sensitively on a central problem, musters his good will and resistances, and the symptoms disappear. The psychiatrist permits him to leave *"cured" by repression.*

A patient gets into difficulties at work and goes to a psychiatrist, who helps him to see some of the connections between his attitude toward his boss and that toward his father. He ventilates some of his resentment more or less toward whom it belongs and ultimately leaves treatment *better "adjusted" on the basis of "insight."*

A patient is panicked by the sudden flash of a thought that she wants to kill her child; the psychiatrist interrogates her about her married life; she begins to pour out her bitterness toward the husband on whom she is dependent and toward whose self-preoccupation she has been passively submissive. Ultimately, she forms a dependent relationship to the psychiatrist, who continues to see her from time to time. Her obsessive thoughts disappear with the abreaction of her rage toward her husband. She continues to get along fairly well, with increasingly long intervals between interviews; the kindly psychiatrist, consciously thought of by the patient as a "good friend," becomes a *sustaining transference figure.*

There are other cases in which the therapy ramifies further than this. The technique of "uncovering" that which has been repressed is applied with great sensitiveness and cogency, and many aspects of the personality and its difficulties are laid bare and understood by the therapist, and often by the patient. Some of this is even worked out on the basis of transference reactions. The patient is helped symptomatically and may come to some apparently conclusive view of himself which enables him to leave the treatment with the feeling that a problem has been solved. This may produce results of such degree and duration that, as far as we know, the patient is "cured." Yet psychoanalytic scrutiny will disclose such a "cure" to have been based on an elaborate rationalization, which depends for its effectiveness on what is dynamically a repression of the basic conflict after some partial solution of derivative conflicts has been attained and accepted as a compromise.

These patients have certainly been treated rationally—that is, in terms of the operating forces; that is, dynamically. They have been carried as far as possible: for theoretical reasons, as in the first instance cited, in which the patient could not tolerate more than a smell of his real troubles; and for practical reasons, as with

the last two patients, who were satisfied with what they got, were not in a position to get more, and may possibly have received all that was useful to them. Finally, with especially suitable material, as in the last-mentioned class of clinical situations, there has been really "intensive" work done, and the patient has attained some kind of a new synthesis. All this is socially worth while and requires creative effort from the psychiatrist, which is justifiably gratifying. But none of it is psychoanalysis.

The last type of case seems to make this issue especially murky. The psychotherapist is able to point to the fact that transference has been dealt with, unconscious attitudes have been demonstrated, and even traced to early sources, and the function of symptoms has been understood. It looks like psychoanalysis, but it is not. What is the difference?

A metaphor may be helpful in this connection. Let us look upon a complex chemical reaction. Assuming that all things remain equal, once it is under way, it will continue to the end until it has reached a final state of dynamic equilibrium. Transitional to this state, many intermediate reactions will have occurred, and many intermediate compounds will have been synthesized and broken down. At any given point in the reaction, changes in temperature or pressure, or the addition of a catalyst or of some foreign substance, will modify the reaction, will slow it down or halt it, or speed it up or explode it, or change the end point at which equilibrium is attained. The relationship between a therapist and a patient, if dynamically oriented, can be seen from this point of view. Psychotherapy is not oriented toward an end point in the interaction between therapist and patient which approaches a final dynamic equilibrium. Psychoanalysis is oriented toward such an end point and, in contrast to psychotherapy, is potentially capable of attaining it.

As I have previously indicated, the psychoanalytic reaction is the transference neurosis, the recapitulation of the pathogenic infantile part in the relationship to the analyst. The end point is the resolution of that neurosis. The technique is directed toward the establishment of the reaction and the maintenance of the optimum conditions of temperature, pressure, and catalysis for its completion. In contrast, psychotherapy, whether from necessity or from choice, will bring the reaction to an end at any point of stability. Thus, psychotherapy must of necessity intervene, contribute, and manipulate. It must be more or less active. It does not work with the transference neurosis as a process. In contrast, psychoanalysis is entirely dependent on the transference neurosis. Dealing interpretively with the resistances and the manifestations of the transference neurosis, it must be more or less passive. Psychotherapy is opportunistic of necessity. Psychotherapeutic techniques, therefore, can be as flexible as the goal-limited orientation requires, and as brilliantly improvised as the genius of the therapist will permit. It can and does employ tactics of penetration. Psychoanalysis has the long-time goal of reconstruction. As Freud has said, it sets up a process which does not cease with the last analytic session, but continues to act so that ego transformation continues.[7] This makes analysis dependent upon a strategy of infiltration.

No one has stated this better than did Robert Waelder at a meeting in Chicago in 1943:

7. Freud, S.: Analysis Terminable and Interminable, Internat. J. Psycho-Analysis **18**:373, 1937.

We are compelled to eliminate short-circuit interpretation in favor of an inching downward and backward from a broad base of character study with a view to arriving at more exact reconstructions of unconscious (guiding) fantasies and of the whole process of the neurotic career. The ultimate technical ideal . . . is to actually transform the neurosis into its earlier stages, and finally into the precipitating conflicts—to roll the process of neurosis back along the path of its development.[8]

The spectrum of therapeutic problems includes cases to which analysis cannot be applied, cases which cannot be treated in any other way with hope of success, cases which benefit from psychotherapy and should not be analyzed, and cases which benefit from psychotherapy but which could have been analyzed; the spectrum of therapists extends from able analysts who cannot do psychotherapy to brilliant psychotherapists who cannot do analysis. None of these facts casts a shadow on the others. The therapeutic impulse led to the discovery of psychoanalysis, and psychoanalysis has given it a scientific rationale. Psychoanalysis as a scientific method of therapy can be enriched by intuition and art. But it cannot depart from its technical dependence on the fact of the transference neurosis and the resistances and still remain psychoanalysis. Psychotherapy as an artistic and intuitive help-giving procedure can be sharpened by scientific knowledge. It need not mimic psychoanalysis (as in the hands of some it seems to) to validate its usefulness in achieving limited goals. There is room in psychiatry, as in medicine, for both significant amelioration and radical cure.

However, psychoanalysis is not simply a chapter in the therapeutics of psychiatry. It has provided psychiatry with a genetic, a dynamic, and an interpretive point of view. It is a body of basic knowledge and basic principles which are relevant to psychiatry and medicine, on the one hand, and to the social sciences, on the other. Because this has been so widely recognized and apparently accepted in this country, psychoanalysis has attained a goal which Freud had only hoped for. Unfortunately, assimilation is producing some of the effects which denigration failed to do.

In recent years there has been a growing tendency to repudiate psychoanalysis as a therapeutic method and to propose various modifications. These derivatives have their place in the evolution of psychiatry, but none has yet established its validity as a successor to psychoanalysis. I have attempted to establish the fact that psychoanalysis, as a unique method of treatment, is inseparable from psychoanalysis as a refined instrument of psychological research, that psychoanalytic knowledge is the basic science of modern psychiatry, and that psychoanalytic research continues to be the only possible source of that knowledge. Psychoanalysis as technique can survive only in psychoanalysis as therapy. "Modified methods" are not psychoanalytic technique and do not give access to comparable information about the unconscious and its forces. Modern dynamic psychiatry can survive and continue to develop only if psychoanalysis survives as such and continues to develop.

8. Waelder, R.: Present Trends in Psychoanalytic Theory and Practice, Year Book of Psychoanalysis, New York, International Universities Press, 1945, Vol. 1.

THE SUPPLEMENTARY MOTOR AREA OF THE CEREBRAL CORTEX

A Clinical and Experimental Study

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JUST IN front of the motor area of the cerebral cortex of man there is a supplementary representation of movements. This supplementary area is rather well circumscribed and is situated largely within the longitudinal interhemispheral fissure (Fig. 1). During the past several years we have seen a number of patients whose difficulties have necessitated surgical exploration and cortical stimulation within the longitudinal fissure. The findings cast new light upon the problem of cortical representation of motor and sensory function.

This paper is an analysis of our observations on the properties of the superior and mesial intermediate precentral cortex in man. The results of local electrical stimulation and the patterns of focal seizures due to discharge in the area are presented, and an attempt is made to interpret the findings in terms of function. In addition, the results of an experimental approach to the analogous area in monkeys is reported.

HISTORICAL NOTE

The function of the cortex which lies anterior to the motor area had elicited a great deal of interest, even before the demonstration by Campbell [1] of the distinctive anatomic properties of the intermediate precentral area. Munk, cited by the Vogts,[2] had foreshadowed Campbell's suggestion that in this region resided Jackson's highest level of representation of movement. The experimental evidence, which was already considerable because of the work of Munk,[3] Horsley and Schäfer,[4] and

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From the Department of Neurology and Neurosurgery, McGill University, and the Montreal Neurological Institute.

Read at the Seventy-Fourth Annual Meeting of the American Neurological Association, Atlantic City, N. J., June 15, 1949.

1. Campbell, A. W.: Histological Studies on the Localization of Cerebral Function, London, Cambridge University Press, 1905.

2. Vogt, C., and Vogt, O.: Zur Kenntnis der electrisch erregbaren Hirnrinden-Gebiete bei den Säugetieren, J. f. Psychol. u. Neurol. **8**:277-456, 1907.

3. Munk, H.: Über die Functionen der Grosshirnrinde. Gesammelte Mitteilungen aus den Jahren 1877-80, mit Einleitung und Anmerkungen, Berlin, A. Hirschwald, 1881.

4. Horsley, V., and Schäfer, E. A.: A Record of Experiments upon the Functions of the Cerebral Cortex, Phil. Tr. **179**:1-45, 1888.

Grünbaum and Sherrington,[5] and which has since been enlarged upon by the Vogts [6] and others, and, in man, by Foerster,[7] has served to deny to the intermediate precentral area the function ascribed to it by Campbell. At the same time, however, this evidence has firmly established the importance of this cortex in the control of posture and movement.

METHODS

In Human Subjects.—The mesial and superior intermediate precentral cortex was stimulated in 24 patients. These cortical explorations were carried out for relief of focal cerebral seizures, tumor, involuntary movements, and pain. Local analgesia (dibucaine [nupercaine®]) was used in all instances. Some of the patients were given thiopental (pentothal®) and nitrous oxide during the surgical exposure but were allowed to awaken before stimulation was carried out. In one patient, a child, stimulations were carried out with the subject under thiopental anesthesia.

In each case a modified Rahm stimulator was used for cortical stimulation at 60 cps, while the intensity was oftenest between 1 and 3 volts.[8] In order to reach the mesial surface, it was

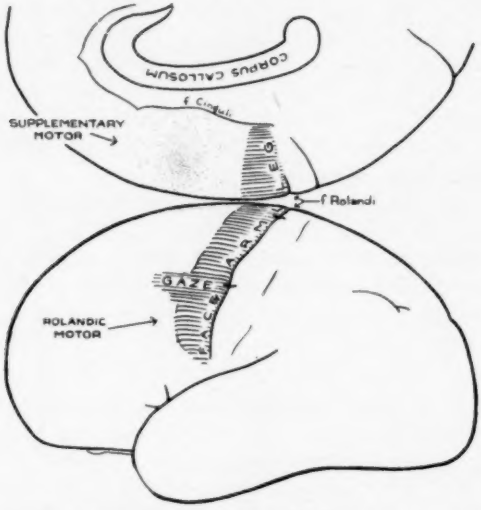

Fig. 1.—The convex and mesial surfaces of the left hemisphere viewed on the same plane. The location of the supplementary motor area and its topographic relationship to the primary motor cortex are shown.

necessary to separate arachnoid granulations from the dura and sagittal sinus and to retract the hemisphere from the falx. We are not aware of any trauma or impairment of circulation as a result.

5. Grünbaum, A. S. F., and Sherrington, C. S.: (*a*) Observations on the Physiology of the Cerebral Cortex of Some of the Higher Apes, Proc. Roy. Soc., London, s.B **69**:206-209 (Nov.) 1901; (*b*) Observations on the Physiology of the Cerebral Cortex of the Anthropoid Apes, ibid. **72**:152-155 (June) 1903.

6. (*a*) Vogt and Vogt [2]; (*b*) Allgemeinere Ergebnisse unserer Hirnforschung, J. f. Psychol. u. Neurol. **25**:277-462, 1919.

7. Foerster, O.: Motor Cortex in Man in the Light of Hughlings Jackson's Doctrines, Brain **59**:135-159 (June) 1936.

8. The intensity as used here is the voltage setting on the Rahm instrument and represents average voltage. The peak voltage is higher than this.

In many cases the stimulations were carried out while electrocorticograms were being made. It was thus possible to be sure that the responses were the result of focal stimulation without epileptic after-discharge.

When excision was carried out, the pial banks of the remaining gyri were preserved as carefully as possible, and the removal was limited to the gray matter.

In Monkeys.—The stimulations were also carried out using local analgesia (dibucaine), sometimes supplemented with thiopental for the surgical exposure. The animal was placed in a special chair designed by Dr. James Ziegler; after the right hemisphere was exposed the animal was turned on his side and the brain allowed to fall away from the falx. It was necessary to clip and divide several veins passing from the brain to the sagittal sinus in the region to be stimulated.

When the condition of the animal permitted, a part of the right hemisphere was removed and a portion of the falx excised without injury to the superior longtitudinal sinus, and the left cingulate gyrus was sucked away, so as to expose the entire left marginal gyrus.

Stimulations were carried out, using both monopolar and bipolar electrodes. A square-wave stimulator was employed.

When experimental lesions were to be made, pentobarbital, sometimes with chloralosane (*o*-chloralose), was given intravenously. The surgical exposure was effected under sterile conditions by well-known techniques, and excisions were made using a fine sucker and were confined, as nearly as possible, to the gray matter.

Some of the stimulation points in each experiment were marked by depositing a small amount of India ink in the cerebral cortex; and when the brains were removed the other stimulation points could be referred to the points marked. The brains were fixed, and the area of interest was studied histologically in serial sections stained with cresyl violet.

EXPERIMENTAL STUDIES ON MONKEYS

Stimulation

Soon after it was discovered that certain portions of the cerebral cortex are electrically excitable, the general topographic arrangement of representation in the motor cortex was learned. Nor was the less easily excited cortex anterior to the Rolandic strip neglected. Ferrier [9] was able to elicit deviation of the head and eyes by stimulation above the superior limb of the arcuate sulcus in monkeys, and he also produced motor effects in the contralateral upper extremity from that part of the cortex which subsequently became known as Area 6.

Munk [2] was apparently the first to discern that arm movements can be elicited by stimulation of the cortex anterior to the motor leg representation on the mesial surfaces of the hemisphere in monkeys. He later described these movements (together, apparently, with the leg responses, posteriorly, and the head-turning effects, anteriorly, on the mesial surface) as more diffuse than those obtained from the convexity, and he concluded that primitive muscle centers are located on the convexity, whereas on the mesial surface a higher order of motor center is present (Munk [2]).

In an intensive investigation of the electrically excitable cortex in monkeys, Horsley and Schäfer [4] confirmed and extended some of the observations of Munk. They summarized their findings in a map (Fig. 2), which has since become well known. In the mesial part of their stimulable cortical arm area, within the inter-hemispheral fissure, they demonstrated movements at the proximal joints (shoulder and elbow) more readily than movements of the more distal parts, and flexor responses were more easily elicited than extensor ones. They considered this mesial area to be an upward extension of the primary motor arm area, as is shown in their map.

9. Ferrier, D.: Functions of the Brain, London, Smith, Elder & Co., 1876.

C. and O. Vogt [6] added greatly to our knowledge of the representation of movement in the cerebral cortex. Their experiments, carried out in monkeys over a period of many years, and summarized in 1919, were significant both because of their careful physiologic observations and because they correlated these findings with anatomic study. Their results, charted in Figure 3, may be summarized as follows:

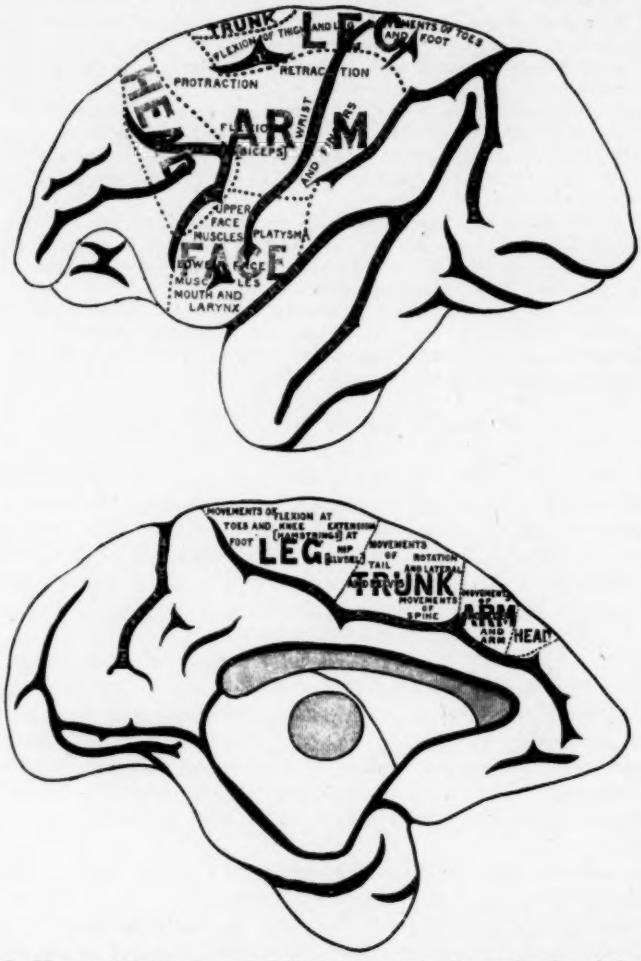

Fig. 2.—Maps used by Horsley and Shäfer [4] to summarize the results of cortical stimulation in Cercopithecus monkeys.

1. In the Betz-cell area (Area 4) stimulation produces localized movements of the various parts of the body. These parts are arranged in the order indicated on their chart. These movements were considered primary movements for Area 4, and the area itself, a primary motor field.

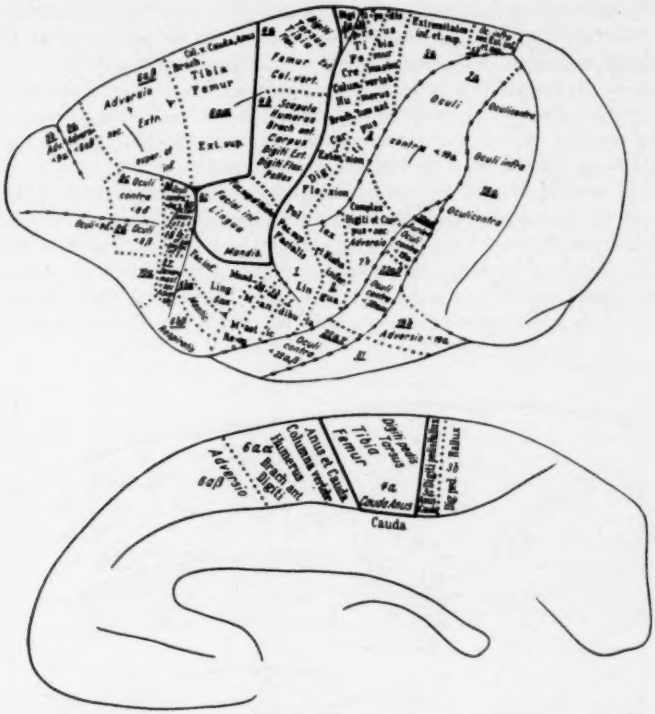

Fig. 3.—The Vogts's map,[6b] summarizing their anatomic and physiologic observations in Cercopithecus monkeys.

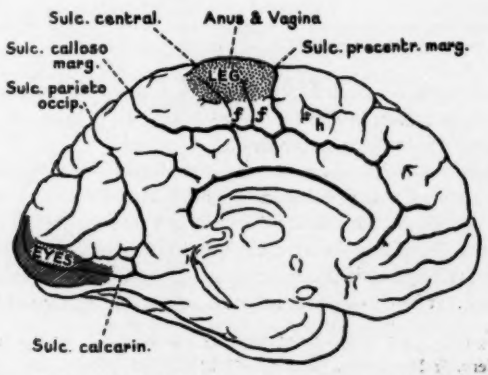

Fig. 4.—A view of the mesial surface of the brain of a chimpanzee, illustrating observations of Grünbaum and Sherrington.[5b] Here, *s* indicates area for movement of the shoulder and chest wall; area *h*, for movement of the hand. These points lie in an area which must correspond to the supplementary motor representation.

2. In the posterior part of the agranular cortex (Area 6a α), stimulation produced movements resembling those elicited from Area 4, and at higher threshold more highly organized and complex movements, including adversion, resulted.

The fine movements, which could be abolished by superficial incision of the cortex between the point stimulated and Area 4, were considered primary for area 6a α, and the area itself was called a secondary motor field. The responses at higher threshold were not abolished by incision, as described.

In that portion of area 6a α within the interhemispheral fissure on the mesial surface of the hemisphere, they observed a topographic arrangement of representation of movements of the trunk and upper extremity, as indicated on their map (Fig. 3). The more proximal movements of the arm were elicited more posteriorly, whereas digital movements were provided more anteriorly. The Vogts did not distinguish this mesial area as of any special functional significance, as had Munk.[2]

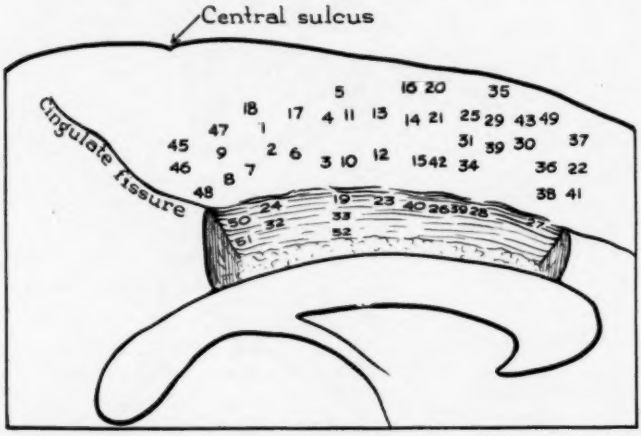

Fig. 5 (Experiment P. 50.113).—The mesial surface of the left hemisphere of a green monkey. The cingulate gyrus has been removed to expose the inferior surface of the marginal gyrus. The numbers represent points of stimulation, as described in the text.

3. The anterior part of Area 6 (6a β) yielded, upon stimulation, only the complex movements described; and these were considered primary for this area. The area itself was called a tertiary motor field.

Since the Vogts's publication, renewed cytoarchitectonic study of the motor area in monkeys by Denny-Brown and Evans, as reported by Denny-Brown and Botterell,[10] and by Von Bonin and Bailey [11] has shown that the Betz-cell area (Area 4, or Area FA) extends farther forward than had hitherto been believed. Therefore, although the Vogts's observations cannot be questioned, their systematized account is in need of revision. It is also apparent that in subsequent studies of the responses of

10. Denny-Brown, D., and Botterell, E. H.: Motor Functions of the Agranular Frontal Cortex, A. Res. Nerv. & Ment. Dis., Proc. (1947) **27**:235-345, 1948.

11. Von Bonin, G., and Bailey, P.: Neocortex of Macaca Mulatta, Illinois Monographs in the Medical Sciences, Vol. 5, No. 4, published by the University of Illinois under the auspices of the Graduate School, Urbana, Ill., University of Illinois Press, 1947.

Area 6 [12] some of the results were obtained from stimulation of the anterior portion of the primary motor area (Area 4).

The cortex of the mesial surface of the hemisphere has not been extensively explored in anthropoid apes. Grünbaum and Sherrington [5b] (Fig. 4) described a few movements of the upper extremity and chest wall elicited by stimulation of the cortex on the mesial surface anterior to the leg subdivision of the motor area. The synergies which Hines [13] produced by stimulating Area 6 in the chimpanzee were apparently elicited from the convexity of the brain.

In our hands, stimulation of the cortex, with particular attention to the mesial surface anterior to the leg, tail, and trunk subdivisions of the motor area, was carried out in 11 monkeys (Macaca mulatta and Cercopithecus aethiops sabaeus).

Before summarizing our results, we present the protocol of a single experiment.

Results of Stimulation of Cortex of Left Hemisphere

Voltage	Points of Stimulation	Results
2-3	1-11, 17, 18, 45, 46, 49, 50	Movements of tail and/or lower trunk
3	12	Extension of right knee
3	13	Tightening of grip of right hand
		Extension of right elbow
2.6	14, 15, 16	Extension of right elbow and of wrist
	19	Extension of right elbow and of wrist
3	20, 21	Extension of right wrist and pronation of arm
	21, repeated	Short seizure characterized by clonic extension of right knee; clonic seizure involving movement on restimulation of same point at 4 volts
	24	Extension of right leg; movement of tail
	25	Extension of right wrist
	26	Extension of flexed right leg at thigh and knee, followed by flexion of thigh and leg, extension of digits of foot, and rotation of the trunk; flexion response observed first when stimulation was begun while the leg was extended
	25, repeated	Extension of right wrist and elbow
2	27	Flexion of right leg and flexion of digits of foot, followed by rotation of trunk and extension of leg
	28	Flexion of right thigh and leg
2.6	29	Extension of right wrist and release of grasp
3	30	Dorsiflexion of right foot; flexion of thigh and leg and rotation of lower trunk
5	31	Extension of fingers of right hand; extension of right elbow
3	32	Extension of right thigh and leg; movement of tail
	33	Flexion of right thigh, leg and digits of foot
	34, 35	Extension and abduction of fingers
	36	Same response as at point 30
	37	Eyes deviated to right
	38	Alternating flexion and extension of right thigh and knee
3.2	40	Same response as at point 26
5	41	Flexion of right thigh and leg
4.2	42	Extension of fingers of right hand, followed by extension of right elbow and of right knee
3	43	Extension and spreading of fingers of right hand, followed by external rotation of right arm
	44	Extension of fingers of right hand and extension of elbow
4	52	Extension of fingers of right hand; flexion of right thigh and extension of knee followed by a seizure

EXPERIMENT P. 50. 113.—Cercopithicus aethiops sabaeus. March 1, 1950 (Fig. 5).

A craniotomy was performed on the right side with the monkey under thiopental anesthesia, after the scalp had been infiltrated with dibucaine solution (1:2,000). A portion of the right hemisphere was removed, and part of the falx was excised, sparing the superior longitudinal sinus and exposing the mesial aspect of the left hemisphere. A portion of the left cingulate gyrus was sucked away, so that the inferior pial bank of the marginal gyrus was exposed. By this time the animal had awakened from the effect of the thiopental. A square-wave stimulator was used at 60 cps and a pulse duration of 3.2 msec. Results of stimulating the numbered points on the cortex of the left hemisphere (Fig. 5) were as shown in the table.

12. Bucy, P. C.: Electrical Excitability and Cyto-Architecture of the Premotor Cortex in Monkeys, Arch. Neurol. & Psychiat. **30**:1205-1225 (Dec.) 1933.

13. Hines, M.: Movements Elicited from Precentral Gyrus of Adult Chimpanzees by Stimulation with Sine Wave Currents, J. Neurophysiol. **3**:442-466 (Sept.) 1940.

Threshold.—In unanesthetized animals the threshold for elicitation of responses from stimulation of the mesial surface, anterior to the motor area, is very slightly higher than that of the primary motor area. The threshold of the mesial area is, however, more easily raised by deterioration in the condition of the animal and by anesthesia.

Movements of Upper Extremity.—Immediately anterior to the portion of the cortex on the mesial surface from which trunk and tail responses are elicited in the green monkey, and leg and tail responses are found in the macaque, there is a region which yields, upon stimulation, movements of the contralateral upper extremity. This region occupies the mesial and inferior surfaces of the marginal gyrus and extends for a distance of approximately 1 cm. in its anteroposterior dimension. In its posterior part flexor responses in the fingers and hand, pronation of the hand, extension of the elbow, and, less often, depression of the shoulder and flexion of the elbow are elicited. More anteriorly, stimulation causes extension and abduction of the fingers and extension of the wrist. Oftenest, the responses involve distal musculature, and frequently it is with prolonged stimulation that the more proximal movements occur.

That portion of the mesial cortex from which hand extension is obtained is considerably larger than the part which yields flexion, and the latter is represented by a narrow band.

If the observer's finger is placed in the palm of the animal's hand in such a way as to elicit a voluntary grasp response, he can sometimes feel a tightening or a relaxation of grip, without visible movement, depending upon the point stimulated.

When, after the responses of specific points on the mesial surface have been outlined, the primary motor arm area is excised, hand movements are no longer elicitable from the mesial cortex, but at higher threshold more proximal movements can be produced from this region.

Movements of the Lower Extremity.—In the anterior part of the mesial excitable arm area dorsiflexion of the foot frequently accompanies the extensor responses in the hand, while inferiorly and anteriorly isolated leg responses become manifest. Isolated movements of the lower extremity are obtainable from the inferior bank of the marginal gyrus, in the depths of the cingulate fissure, beneath the arm representation.

On a few occasions, when both hemispheres were intact, we have seen bilateral leg movements associated with trunk responses elicited in the anterior portion of the supplementary motor area near the cingulate fissure.

Other Motor Effects.—We have searched for a face representation in this area but have been unable to obtain responses in the face, except for the symmetrical facial responses obtainable from the mesial surface of the cingulate gyrus. Stimulation of the superior surface of the cingulate gyrus, after removal of the marginal gyrus, has failed to produce face responses.

Vocalization and inhibition of voluntary movements, obtainable, as we shall see, from this region in man, are not produced under the conditions of these experiments in the monkey.

Head rotation and eye responses are obtainable anteriorly from the mesial surface, and the area from which these are obtained is overlapped by the area for hand and foot responses. Frequently, however, the threshold for the head deviation

is higher than that for the movements of the extremities. With deterioration in the condition of the animal or with deep anesthesia, the threshold for movements of the extremities goes up, and the head and eye responses only can be obtained.

The supplementary motor area in monkeys occupies the mesial surface of the marginal gyrus and that portion of the marginal gyrus which is buried with the cingulate fissure. It apparently ends at the very depths of this fissure, for we have stimulated the superior surface of the cingulate gyrus without producing similar effects. Posteriorly, on the mesial surface of the marginal gyrus, the supplementary motor area is limited by the tail and leg subdivisions of the primary motor area. Anteriorly, the eye-turning field forms a boundary, and, above, the brow of the interhemispheral fissure forms an approximate border.

Excision

In their study of reflex grasping associated with lesions of the frontal lobe, Richter and Hines [14] showed that a lesion of Area 6 of Brodmann caused transient contralateral reflex grasp in macaques. These authors clearly stated that in order to result in this sign the lesion must involve the most dorsal and the mesial part of the hemisphere and that superficial lesions in the lateral part of Area 6 are ineffectual. They also showed that excision of other parts of the frontal lobe do not cause the grasp reflex. These findings were quickly confirmed by Fulton, Jacobson, and Kennard [15] and were extended by them to other species of monkeys, as well as to the baboon and the chimpanzee. Since this time, reflex grasping has been considered a specific sign of injury to the cortex of Area 6, and the observation that only when the mesial surface of this area is damaged does this sign develop has been overlooked.

The other effect of isolated unilateral excision of Area 6 is transient awkwardness of the contralateral extremities.[16] Whether or not spasticity is present after such an experimental lesion is controversial.[17]

The presence of an excitable motor zone, the supplementary motor area, within the region where damage leads to reflex grasping, and, especially, the prominence of release of grasp, extension, and spreading of the fingers as a response to stimulation of this motor zone, suggested that reflex grasping might be a specific symptom of damage to the supplementary motor area rather than to the whole of the cytoarchitectural area (Area 6) of which it forms a part. The experiments of Richter and Hines had already shown the importance of destruction of the mesial surface of Area 6 in the production of grasping. These investigators did not, however, limit their excisions to that portion of the cortex which lies above the cingulate fissure, and their experimental lesions extended deep into the white matter.

14. Richter, C. P., and Hines, M.: Experimental Production of the Grasp Reflex in Adult Monkeys by Lesions of the Frontal Lobes, Am. J. Physiol. **101**:87-88 (June) 1932; Production of the "Grasp Reflex" in Adult Macaques by Experimental Frontal Lobe Lesions, A. Res. Nerv. & Ment. Dis., Proc. (1932) **13**:211-224, 1934.

15. Fulton, J. F.; Jacobson, C. F., and Kennard, M. A.: Note Concerning the Relation of the Frontal Lobes to Posture and Forced Grasping in the Monkey, Brain **55**:524-536 (Dec.) 1932.

16. Fulton, J. F., and Kennard, M. A.: Study of Flaccid and Spastic Paralyses Produced by Lesions of the Cerebral Cortex in Primates, A. Res. Nerv. & Ment. Dis., Proc. (1932) **13**:158-210, 1934.

17. Fulton and Kennard.[16] Hines, M.: Anterior Border of the Monkey's (Macaca Mulatta) Motor Cortex and the Production of Spasticity, Am. J. Physiol. **116**:76 (June) 1936.

We have undertaken, in two experiments, to determine whether or not the grasp reflex in monkeys is a sign of injury, in particular, to the mesial excitable region—the supplementary motor area.

An abstract from the protocol of one of these experiments follows.

EXPERIMENT P. 50. 133.—Immature female green monkey (Cercopithecus aethiops sabaeus), weighing 2 kg. (Fig. 6).

First Operation (March 13, 1950, 10 a. m.).—With the patient under anesthesia produced by chloralosane (40 mg.) and pentobarbital sodium (10 mg.), an osteoplastic craniotomy was performed on the right side. A superficial lesion was made by sucking away the cortex mesial to the superior limb of the arcuate sulcus, and almost to the midline. The posterior border of the ablation was in the coronal plane of the anterior extent of the superior precentral sulcus, and anteriorly the lesion extended just oral to the anterior extent of the superior limb of the arcuate sulcus. The superior bank of this sulcus was removed down to its depth (Fig. 6).

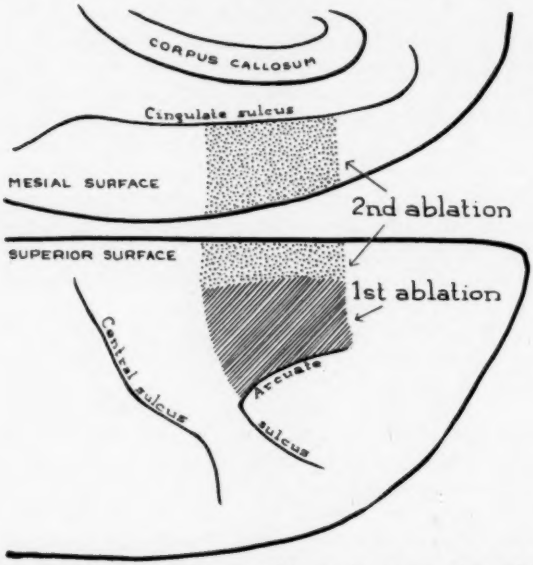

Fig. 6 (Experiment P. 50.133).—Diagram of the mesial and superior surfaces of the right hemisphere of a green monkey, showing the two experimental lesions. At the first operation the area indicated by the diagonal lines was excised. The extent of the second excision is indicated by stippling. Reflex grasping did not follow the first operation, but was present when the animal awakened from the anesthesia after the second procedure.

At 2:30 p. m. on the day of operation, the animal seemed drowsy. Movements were tremulous on both sides, but strength was equal and there was no asymmetry of grasp responses on the two sides. Head rotation and eye movements were intact.

On the day following operation the animal was agile in movements about the cage and showed no groping or impairment of movements due to involuntary grasp. The two hands were used equally well, but the right was preferred. There was no asymmetry in grasp responses in the two hands. She was able to release the grasp of either hand.

At no time did this animal show reflex grasping during the postoperative period of observation, which lasted seven days.

Second Operation (March 20).—Chloralosane (40 mg.) and pentobarbital sodium (10 mg.) were given. The wound was reopened. The excision extended mesially and down to the cingulate fissure (Fig. 6).

Upon awakening from the anesthetic, the animal was tremulous in movements and unsteady in stance and gait. When she lay on her right side, the left fingers were clenched. She seemed unable to release the grasp with this hand if the flexor tendons were stretched.

Twelve hours after operation she was active and agile in movements about the cage. She used the right hand, however, for movements requiring dexterity. When an object was drawn down the palmar surface of the right hand, she sometimes grasped the object and sometimes did not. If she grasped it, she frequently let go of it. On the left side, however, the grasp response to this stimulus was invariable, and she seemed unable to release the grasp.

On the day following operation, the observations of the preceding day could be repeated, and she continued to show reflex grasping with the left hand (and, to a less extent, with the left foot) until the 10th postoperative day.

In the other, similarly controlled, experiment in which the supplementary motor area was excised a like result was obtained.

It has been pointed out by Beiber and Fulton [18] that reflex grasping, which follows bilateral removal of Areas 4 and 6 in monkeys, is altered by the position of the animal in space. It is present, together with groping, in the uppermost extremities when such an animal is placed on its side, and it is depressed or absent in the lowermost extremities. This reflex is also modified by movements of the neck, so that in the tonic-neck-reflex posture, reflex grasping is accentuated on the side of the flexed extremities and depressed in the extended extremities.[19] Thus, reflex grasping has been identified as a component of the righting reflex in primates.

The specific association of this reflex with damage of the supplementary motor area in monkeys suggests that the control which this area exerts over movements of the extremities is related to postural adjustment.

RESULTS OF CORTICAL STIMULATION IN MAN

General Observations

Electrical excitation of the mesial and superior surfaces of the cortex anterior to the precentral gyrus in man produced an unexpected variety of responses—vocalization; movements of the head, face, arms, trunk, and legs; inhibition of voluntary activity; aphasia; eye movements; pupillary effects; cardiac acceleration, and arrest of breathing. The area from which these responses were obtained is indicated in Figure 1.

The threshold for production of these effects was usually higher than that of the postcentral and precentral gyri. Whereas 1 or 1.5 volts, at 60 cps., on the Rahm stimulator, might be required to produce response from the Rolandic cortex, it was usually necessary to employ from 1 to 3 volts in the supplementary motor region. Although some responses were immediate, the latency was, in general, longer in the intermediate precentral area, and one or two seconds frequently passed before any effect was noticeable. On the other hand, latencies of equal duration were occasionally seen in the primary motor area.

Vocalization

Vocalization as a result of electrical stimulation of the precentral gyrus was described initially by Penfield.[20] This response, a continuous, even vowel sound,

18. Beiber, I., and Fulton, J. F.: Relation of the Cerebral Cortex to the Grasp Reflex and to Postural and Righting Reflexes, Arch. Neurol. & Psychiat. **39**:433-454 (March) 1938.

19. Fulton, J. F., and Dow, R. S.: Postural Neck Reflexes in the Labyrinthectomized Monkey and Their Effect on the Grasp Reflex, J. Neurophysiol. **1**:455-462 (Sept.) 1938.

20. Penfield, W.: The Cerebral Cortex in Man: I. The Cerebral Cortex and Consciousness, Arch. Neurol. & Psychiat. **40**:417-442 (Sept.) 1938.

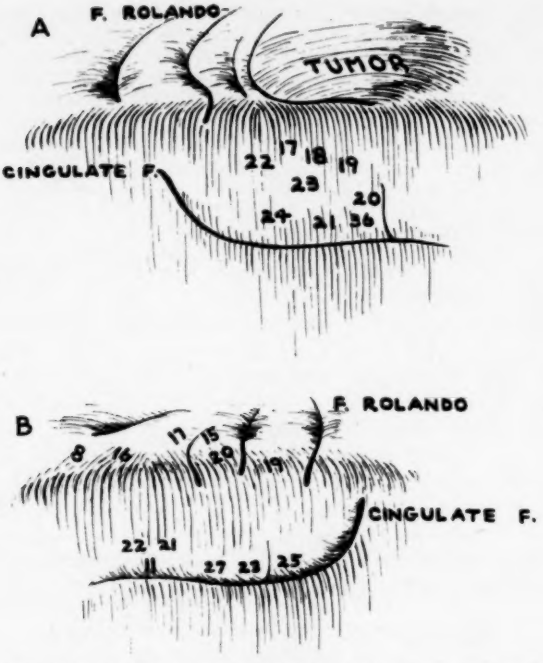

Fig. 7.—*A* (Case 1, K. H.), Mesial aspect of left hemisphere, redrawn from a sketch made at operation. The numbers represent points of stimulation, as shown in the following protocol:

Voltage	Points of Stimulation	Results
2	17	Patient repeated a vocal sound. She explained afterward that she thought she had started to say something and that something had made her stop.
	17	Patient was counting when stimulus was applied. Stimulation arrested speech completely. Patient added, "It raised my right arm."
	18	Patient was counting. Stimulation caused her to vocalize in a continuous sound. She explained afterward that she could not count during stimulation. There was movement of the right arm.
	19	Patient was counting. When stimulation was applied, she made an exclamation and then was silent. Her head turned to the right, and there was movement of the right arm.
	20	While patient was counting backward, stimulation was applied. She stopped counting and resumed it two seconds after withdrawal.
	19	The same stimulation was repeated while patient was counting. A rhythmic vocalization was produced.
	18	When this point was restimulated, without warning, she made an interrupted vocal sound, which sounded like "da da da da."
	21	This point was stimulated while the patient counted. She hesitated, then continued. The right shoulder was drawn posteriorly, and the right leg became extended and raised off the table.
	22	The patient said, "Oh." There was a movement of the body. The patient said afterward that her body seemed to arise, but she did not seem to be doing it. She said she experienced this at the beginning of her attacks.
	23	Patient vocalized.
	24	Patient's head turned to the right and raised off the pillow. Her mouth closed and pulled toward the left.
Near	24	Right index finger and thumb were approximated, and her hand became rigid.
	17	When this procedure was repeated, patient was unable to name objects she was shown. This lasted beyond the time of stimulation.
	21	Vocalization.
	36	Stimulation caused her to hesitate and to vocalize slightly. This was repeated. She was unable to count or to name objects until more than a minute later. When asked what her first name was, she said "Oh."

(Legend continued on next page)

was elicited from various points in the face subdivision of the motor area. The response continued for the duration of stimulation or until maximum expiration was reached. Then there was a pause for breathing, after which the sound was resumed. Penfield and Rasmussen [21] reported 51 cases of vocalization resulting from stimulation. These responses were obtainable from the entire face subdivision of the Rolandic gyri. With about one-half the responses there were face movements.

A different kind of vocal response, elicited from the mesial surface of the frontal lobe anterior to the leg subdivision of the motor area, was reported by Brickner.[22] His patient vocalized in a repetitive manner upon stimulation and could be caused to repeat letters when the stimulus was applied while she was reciting the alphabet.

21. Penfield, W., and Rasmussen, T.: Vocalization and Arrest of Speech, Arch. Neurol. & Psychiat. **61**:21-27 (Jan.) 1949.

22. Brickner, R. M.: A Human Cortical Area Producing Repetitive Phenomena When Stimulated, J. Neurophysiol. **3**:128-130 (March) 1940.

B (Case 2, H. R.), mesial aspect of right hemisphere drawn from a sketch made at operation. Responses to stimulation of the numbered points (Rahm stimulator; 60 cps) were as follows:

Voltage	Points of Stimulation	Results
1	8	Patient said he started to feel as he does when he has a spell—"a little choked up."
2	11	Patient's left arm was flexed; his pupils were dilated widely. When asked what had happened, he said he had had an attack. There was no after-discharge.
1	11	On stimulation for 8 sec. he said, "I feel jittery in my stomach."
	11	Stimulation for 10 sec. caused no relaxation of hand grip; there was slight dilatation of the left pupil.
2	15	Patient said "nothing." Then he added, quite forcibly, "My leg is getting numb. Both."
	16	There was interrupted vocalization. When the stimulation was over, he said, "nothing."
	16	This was repeated while the patient was counting. When he reached 10, he said, "te-eh-eh-eh-eh-eh," repeating the vowel sound six times.
	17	Patient's counting slowed down between 10 and 15, which was the period of stimulation. When asked why he slowed down, he replied that he did not know.
	15	When this point was restimulated, his counting slowed down. There was clonic jerking of the left leg.
	16	This point was restimulated while he was counting. He slowed down, the tone rose; the force of his voice decreased, and then he stopped. On withdrawal, after a little pause, he counted again. There was dilation of the left pupil, and this eye turned upward. (The left was the only eye which could be seen.)
	16	When stimulation was repeated, he said he became a little sleepy.
	15	Repetition of stimulation of this point caused his counting to become faint. There was jerking of the left leg.
3	16	This point was restimulated while the patient was squeezing an observer's hand. There was no relaxation of grip. Presently he vocalized very faintly in an interrupted manner.
	8	Stimulation of this point was repeated. The patient made a retching movement and said he felt nauseated and wanted to vomit.
2	17	Stimulation of this point was repeated. Counting slowed to a practical arrest. When asked why, he said that he did not know.
3	8	This point was stimulated again. He reported a "funny" feeling in his stomach, like an attack.
	21	The patient tried to speak and was unable to do so. When asked why, he said, "I don't know. I got paralyzed, so I could not speak." There were movements of the jaw, as though he were trying to speak during the time of silence.
	21	Stimulation was repeated while the patient was counting. He stopped suddenly. After withdrawal of stimulation he observed spontaneously that he felt like whistling. Stimulation near Point 21 was carried out without warning. His counting stopped, and vocalization, increasing slowly in volume, ensued. Just before vocalization began, he made a facial movement as though trying to whistle. When asked why he did this, he said, "I don't know, sir. I just couldn't help it."
	22	The patient said he felt nervous.
	21	(Restimulation without warning) After a period of movement of the face as though he were trying to form a word, he vocalized slowly and rhythmically.
	21	After a period of 4 sec. there was rhythmic vocalization, increasing gradually in volume. When asked why he made the noise, he said, "I cannot help it."
	26	(This point is not marked. It was between 22 and 21, and above them and on the gray matter, which had been cut across by the excision.) The patient vocalized in a rhythmic manner.
	27	Rhythmic movement of the leg occurred, with after-discharge.

Our experience is as follows: Vocalization was produced 15 times in seven patients from stimulation in the mesial intermediate precental region. The most characteristic response was a rhythmic, or intermittent, sound but instantaneous exclamation, continuous prolongation of a vowel sound, and the repetition of a word or of a meaningless syllable, or combination of syllables, have been observed as well. Periodic changes in pitch and volume of the vocalized sound have given some of the continuous responses a rhythmic character. Others of the continuous vocalization responses have shown gradual elevation of pitch and reduction of volume.

Associated with these responses have sometimes been seen facial movements involving both sides of the mouth and jaw, movements frequently in rhythm with periodic variations in volume of the sound or with each sound in an intermittent response. In case the patient was counting when the stimulus was applied, the vocalization simply replaced the counting.

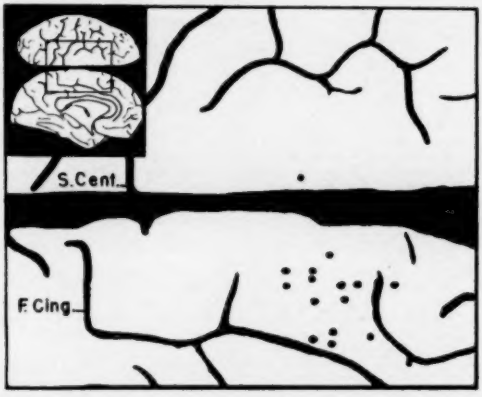

Fig. 8.—Diagram of the superior and mesial surface of the left hemisphere, showing the distribution of points from which vocalization was produced upon stimulation. Results obtained from both hemispheres are shown on the left hemisphere, for convenience.

One patient, K. H. (Case 1; Fig. 7*A*), repeated a vocal sound when Point *17* was stimulated. She explained afterward that she thought she had started to say a word and that something made her repeat. Point *18* was stimulated while she was counting. She stopped counting and vocalized in a continuous sound. She was also counting when Point *19* was stimulated, and this caused her to make a short exclamation and then be silent. A point adjacent to *19* was then stimulated while she was counting, and a rhythmic vocalization ensued. Vocalization responses were similarly produced by stimulating Points *21* and *23*.

Another patient, H. R. (Case 2; Fig. 7*B*), showed similar responses. He was counting and had reached 10 when Point *16* was stimulated. He said "te-eh-eh-eh-eh-eh-eh," repeating the vowel sound about six times. This point was again stimulated while the patient was asked to squeeze the anesthetist's hand. There was a faint vocalization in an interrupted manner but no relaxation of grip. Interrupted vocalization was similarly produced by stimulating Point *21*, and while he vocalized there was movement of the face, as though he were trying to form a word. When stimulation was repeated at Point *21*, there was vocalization after a latency of four seconds. The vocal sound increased in volume, with rhythmic variations. Again, stimula-

tion near Point *21* caused him to make a vocal sound, which slowly increased in volume and was accompanied by movement of the face as though he were trying to whistle. Rhythmic vocalization was also produced at Point *26*, the position of which is explained in the legend of Figure 7*B*.

The location of the stimulation points from which vocalization has been produced in various cases is shown in Figure 8. These points are all plotted, for convenience, on a diagram of the left hemisphere. Actually, these responses were obtained from the right hemisphere in three patients and from the left in four. Most of the responses were elicited from the mesial surface, but one was obtained from stimulation just over the brow of the sagittal fissure on the convex surface of the hemisphere.

The complexities involved in the production of simple continuous vocal responses have previously been emphasized by Penfield [20] and Penfield and Rasmussen.[21] These authors have pointed out that vowel vocalization requires synergistic action of muscles of expiration, of the larynx, and of the jaw and mouth, but that this complexity does not approach that required for speech. Sounds assume meaning and become speech when combined in a conventional pattern of words.

It is not suggested that the complex vocal responses produced by artificial stimulation of the supplementary motor area constitute speech responses. However, modulation of pitch and volume and rhythmicity of vocal sounds are, when associated with conventional meanings, characteristics of speech. Some languages, notably Chinese, might seem to utilize these characteristics to a great extent. These mechanisms, which we have activated by gross artificial stimuli, may, however, under different conditions, be important in the production of the varied sounds which men often use to communicate ideas.

Alteration of Voluntary Activity

General Observations.—Inhibitory effects from stimulation of the motor cortex were recognized shortly after the demonstration of its excitability.[23] However, these negative effects were of localized character. The limited inhibitory effects obtainable from the motor cortex were studied exhaustively by Sherrington and his pupils. The Vogts [6b] described arrest of induced masticatory activity upon stimulation of the frontal eye field in monkeys. Still more widespread inhibitory effects of stimulation have been investigated, principally by Dusser de Barenne and McCulloch,[24] and Dusser de Barenne, Garol, and McCulloch,[25] in monkeys. These investigators described areas which seemed to produce more widespread suppression of distant neuronal activity. Stimulation of these so-called suppressor areas caused decreased excitability of the motor cortex to subsequent stimulation, relaxation of muscular tone, and attenuation of brain waves.

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23. Bubnoff, N., and Heidenhain, R.: Über Erregungs- und Hemmungsvorgänge innerhalb der motorischen Hirncentren, Arch. ges. Physiol. **26**:137-200, 1881-1882.

24. Dusser de Barenne, J. G., and McCulloch, W. S.: Suppression of Motor Response upon Stimulation of Area 4s of the Cerebral Cortex, Am. J. Physiol. **126**:482 (July) 1939; Suppression of Motor Response Obtained from Area 4 by Stimulation of Area 4s, J. Neurophysiol. **4**:311-323 (June) 1941.

25. Dusser de Barenne, J. G.; Garol, H. W., and McCulloch, W. S.: Functional Organization of Sensory and Adjacent Cortex of the Monkey, J. Neurophysiol. **4**:324-330 (June) 1941.

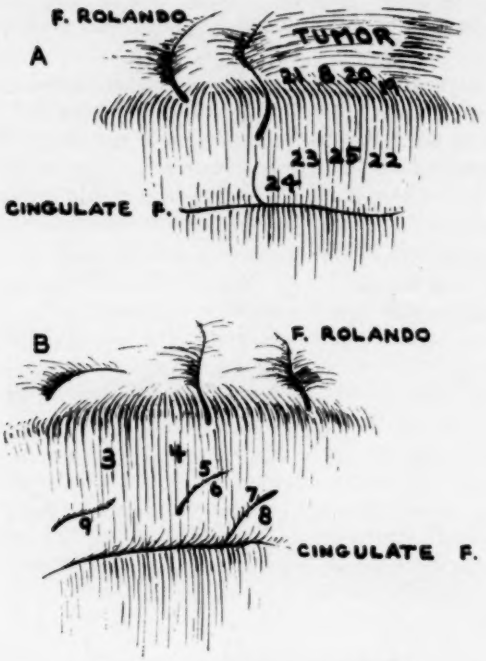

Fig. 9.—*A* (Case 3, L. R.), mesial view of the left hemisphere, elaborated from a sketch made at operation. Responses to stimulation of the numbered points were as follows:

Voltage	Points of Stimulation	Results
1	8	The patient said, "I can't say. I think I am going into a spell." He explained afterward that he could not say what was the matter. When asked why he thought he was going to have a spell, he said, "Because of the haziness that took place in front of my eyes."
2	19	This point was stimulated while the patient was counting backward. He stopped counting after two or three numbers.
	20	The patient was counting. The stimulation was applied when he reached 5. He said, "Six, seven," then stopped. He closed his eyes as though concentrating. Eventually, he began "seven, eight, nine."
	21	The patient was counting. He recited the next two numbers properly and then stopped. When asked why he did not count, he said, "What am I up to?"
	22	When stimulation was carried out at this point, the patient did not reply. Eventually, he said, "The haziness."
	23	The patient gradually began to vocalize in a rhythmic manner. This was associated with twitching of the lower lip and then of the chin. The twitching of the chin was in rhythm with the vocalization.
	24	This stimulation was very brief. The patient did not reply. A little later he said, "It seemed to me I was going into a spell." Dr. André Pasquet observed opening and closing of the right eye.
	25	The patient did not reply for some time. He seemed unable to speak. His eyes closed, and there was rapid twitching of the lids. Eventually he said, "The haziness."

(Legend continued on next page)

In man, specific suppressor areas have not been outlined,[26] although decrease in muscle tone and excitability of the motor cortex were produced in one case by Garol and Bucy.[27] However, Sherrington's inhibition, as well as facilitation, may be produced by stimulation of the sensorimotor strip of Rolando in man, just as in animals.[28]

Arrest, hesitation, and slowing of speech as the result of cortical stimulation have been described by Penfield,[20] Robb,[29] and Penfield and Rasmussen.[21] These effects can be produced in two ways: (1) by stimulation of the face or mouth subdivisions of the sensorimotor strip of either hemisphere, or (2) by stimulatory inactivation

26. Certain stimulation points from which inhibition of Parkinson's tremor and rigidity can be produced have been considered "suppressor." (Hecaen, H.; David, M., and Talairach, J.: L'aire "suppressive" du cortex prémoteur chez l'homme, Rev. neurol. **79**:726-732 (Dec.) 1947. Reid, W. L.: Studies on the Tremor-Rigidity Syndrome: I. Surgical Treatment of Human Subjects, M. J. Australia **2**:481-492 (Oct. 23) 1948. Wyke, B. D.: Suppressor Activity in the Human Brain, Essays in Biology Presented to Arthur Neville Burkitt, Private printing, 1948.)

27. Garol, H. W., and Bucy, P. C.: Suppression of Motor Response in Man, Arch. Neurol. & Psychiat. **51**:528-532 (June) 1944.

28. Penfield, W., and Boldrey, E.: (*a*) Somatic Motor and Sensory Representation in the Cerebral Cortex of Man as Studied by Electrical Stimulation, Brain **60**:389-443 (Dec.) 1937; (*b*) Cortical Spread of Epileptic Discharge and the Conditioning Effect of Habitual Seizures, Am. J. Psychiat. **96**:255-281 (Sept.) 1939. (*c*) Penfield, W., and Welch, K.: Instability of Response to Stimulation of the Sensorimotor Cortex in Man, J. Physiol. **109**:358-365 (Sept.) 1949. (*d*) Penfield, W., and Rasmussen, T.: The Cerebral Cortex of Man, New York, The Macmillan Company, 1950.

29. Robb, J. P.: Effect of Cortical Excision and Stimulation of the Frontal Lobe on Speech, A. Res. Nerv. & Ment. Dis., Proc. (1947) **27**:587-609, 1948.

B (Case 4, R. B.), mesial view of right hemisphere. The drawing is an elaboration of one made at the time of operation. Responses to stimulation, (Rahm stimulator; 60 cps) are indicated as follows:

Voltage	Points of Stimulation	Results
4	3	Patient was counting, and stimulation caused him to stop. This was repeated five times.
3	4	Patient was counting. Stimulation caused him to stop counting and continue a number into a steady sound. This observation was repeated five times.
3	5	There was turning of the head and eyes to the left. (Only the right eye could be seen.)
3	6	Patient was counting. He continued counting when stimulation was applied, but his left arm became raised. He said that his left leg and whole body moved also and that he felt pins and needles in his left leg.
3	7	Patient was counting when stimulation was carried out. He stopped counting. His head and eyes turned to the left. His left shoulder was drawn down, and his left arm was held rigidly.
3	8	Flexion of the left knee.
3	3	Repeated stimulation at this point caused the patient to stop counting. He said he felt weak all over, as though he might collapse.
3	7	When stimulation was repeated, he slowed his counting and then stopped. There was after-discharge. His head turned to the left.
3	9	Patient was counting. His head and eyes turned to the left, and the counting stopped. There was electrographic after-discharge.
3	..	Stimulation just below point 9 caused the patient to report that he had felt as though his whole body were going to jump. No movements were observed.
3	9	Patient was counting, and repeated stimulation caused him to stop. His head turned a little. After withdrawal of stimulation he continued to count. He was then able to reproduce accurately two sentences which the operator had called out during the patient's silence.
5	..	Stimulation of a point between 3 and 4, but somewhat closer to 4, while the patient was counting, caused him to repeat the 3 for a considerable period.
5	..	Stimulation at this point again caused him to stop counting. When asked why he could not count, he said, "I would if I could." When asked why he couldn't, he replied, "I feel too weak."

of one of the specific speech areas of the dominant hemisphere. In this case, true temporary aphasia is produced. Three speech areas which seem to be discrete are situated in the frontal, parietal, and temporal cortex.

Superior Intermediate Precentral Cortex.—Alteration of ability to continue or to initiate voluntary activity resulted from stimulation of 42 points (20 patients) in the mesial superior intermediate precentral region, or supplementary motor area. Because the most frequently employed test situation was counting or ability to reply, arrest of counting and inability to reply were the most frequent responses. Slowing and hesitation of speech were observed as well. However, arrest, hesitation, slowing, or inability to initiate other phasic motor activity was produced with equal ease. As is the case with speech arrest resulting from stimulation of the sensorimotor strip, these responses were often associated with movements of the mouth. These movements resembled attempts at speech. Arrest of voluntary performances was sometimes associated with changes in gaze or in pupillary size or with some alteration of bodily posture.

In one patient (C. L.) stimulation of a point (Point *25*) in the supplementary motor area produced inability to respond. The surgeon called "25, 26, 27." After the electrode was removed, the patient began to speak and was able to remember and to repeat these numbers accurately. He said, "I could hear what you were saying, doctor. I knew what I wanted to say, but I just couldn't."

In another patient, L. R. (Case 3; Fig. *9A*), stimulation at Point *19* while he was counting backward caused him to stop after continuing to count two or three numbers. Again, he was counting and had reached *5* when Point *20* was stimulated. He said, "Six, seven"; then stopped. He closed his eyes as though concentrating. When the stimulus was withdrawn, he continued "seven, eight," etc. Similarly, counting was interrupted by stimulation at Point *21*, and he was unable to reply during stimulation at Points *22*, *24*, and *25*.

When Point *3* was stimulated in another patient, R. B. (Case 4; Fig. 9*B*), counting was arrested. This was repeated five times. Similar arrest occurred when Point *7* was stimulated; but this time his head and eyes turned to the left, his left shoulder was drawn down, and his left arm was held rigidly. Turning of the head to the left and arrest of counting were caused by stimulation at Point *9*. When this stimulation was repeated a second time, he was able to reproduce accurately two sentences which the operator had called out during the patient's silent period.

In another patient, A. T. (Case 5; Fig. 12), when a point in the right hemisphere (Point *19*) 3 cm. anterior to the top of the central sulcus, and at the very brow of the sagittal fissure, was stimulated, she made a little sound. When this was repeated while she was counting, she slowed down. The patient was then asked to approximate the index finger and thumb of the right (ipsilateral) hand repeatedly. When stimulation was carried out at Point *19*, there was momentary slowing of finger movements. When the electrode was removed, the movements quickened again. When she was then instructed to make similar movements with the left hand, this movement was arrested during stimulation and was resumed four seconds later, upon withdrawal of the electrode.

The inhibition responses are charted in Figure 10. These have been plotted on a map of the left hemisphere, although this kind of response may be obtained with equal ease from the dominant and the nondominant side.

The nature and significance of this powerful inhibitory state which can be produced from stimulation of the supplementary motor area [30] deserve consideration.

30. We have recently seen a similar effect in a patient (G. A.) upon stimulation just above the parietal speech area. We have also recently observed that stimulation of "speech-arrest" points in the lower Rolandic region inhibits voluntary movements of the extremities. This suggests that this property of the supplementary motor area may be shared with other specific regions of the brain.

Reports from the patients indicate that consciousness was not impaired during these stimulations. After cessation of stimulation one patient was able to repeat numbers which had been called aloud by the surgeon, and many indicated that they knew what they wanted to say but could not.

It is also evident that the loss of function during stimulation is not due to simple electrical inactivation of the stimulated cortex itself, for removal of the area does not have the same effect. The same could be said of stimulation of the mouth area in the lower sensorimotor strip. Stimulation may make it impossible for the patient to speak, but excision does not greatly affect the ability to speak.

The deficit, therefore, seems to depend upon the activation of local ganglion cells which interfere, through their neuron projections, with more distant associated mechanisms. Whether these neurons are normally devoted to the function of inhibition or whether, when activated in this unphysiologic manner, they somehow dis-

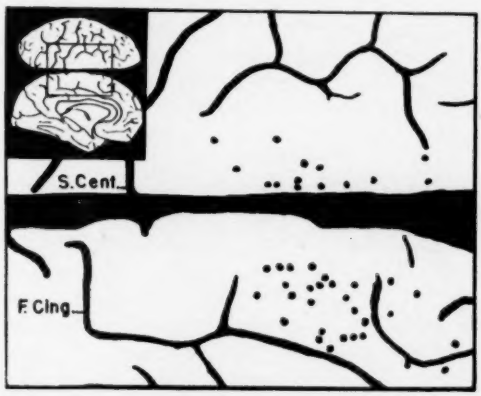

Fig. 10.—Diagram of the superior and mesial surfaces of the portion of the left hemisphere showing the position of points of stimulation from which inhibition of voluntary activity was produced. These results, obtained from both hemispheres, are all plotted, for convenience, on a diagram of the left hemisphere.

organize the motor mechanisms to which their function is normally related, must be left undecided. It would be unfortunate to employ the word "suppressor" to describe this region in the present state of our knowledge.

Movements of the Extremities and Body

The experimental evidence in man and other primates has emphasized the control which the "intermediate" cortex can be made to exert over the movement and posture of the trunk and limbs. This emphasis is embodied in the various concepts which have developed regarding the area—"frontal adversive field," "premotor area," etc. We have reviewed, in a previous section, the contributions of others, as well as our own experience, in stimulating this region in experimental animals. Before we describe the motor responses which we have obtained in human subjects, evidence bearing more directly on man should be reviewed briefly.

Review of Literature.—Adversive Movements and Synergies: Foerster [7] found that stimulation of Area 6a β [31] produced adversive movements of the head, eyes and trunk, as well as flexor and extensor synergies of the contralateral arm and leg (Fig. 11). After removal of the motor area proper he could still produce the same movements, which he likened to the gross abilities of hemiplegic extremities. In the absence of the motor area, adversive responses were obtained from Area 6a α [31]

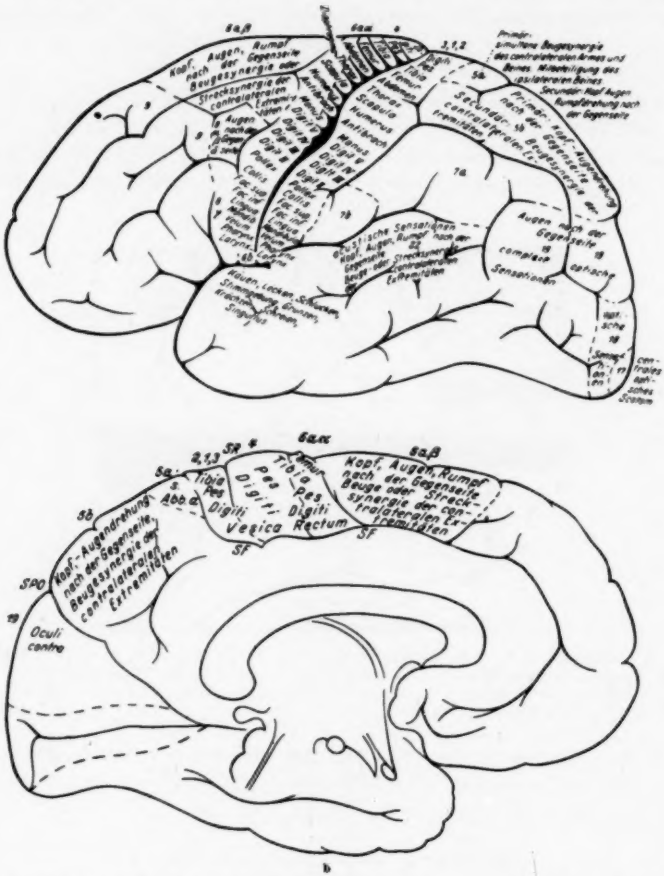

Fig. 11.—Convex and mesial surface of the left hemisphere, summarizing Foerster's observations from stimulation of the cortex in man (Foerster, O., in Bumke, O., and Foerster, O.: Handbuch der Neurologie, Vol. 6, Berlin, Julius Springer, 1936).

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31. The designation of cytoarchitectonic areas used by Foerster referred to the cytoarchitectonic study of C. and O. Vogt (Sitz und Wesen der Krankheiten im Lichte der topistischen Hirnforschung und des Variierens der Tiere, J. f. Psychol. u. Neurol. **47**:237-457 [April] 1937).

The map used by Foerster (Fig. 11) is that used by the Vogts to summarize their histologic studies, which were never published in detail.

also. The prominence of the adversive responses to his stimulations led to his concept of "the frontal adversive field."

Penfield and Boldrey,[28a] employing less strong stimulation of the human cortex and excluding the local seizures sometimes produced by the stimulus, found that adversive gaze was produced only in the eye field which is precentral in a mid-frontal zone (Fig. 1), but failed to obtain Foerster's turning movements in the superior intermediate cortex. It must be admitted, however, that they did not include in their explorations the cortex that lies within the median longitudinal fissure. It may be assumed, also, that Foerster's experience in stimulating this portion was small, inasmuch as he did not produce vocalization.

Grünbaum and Sherrington [5a] produced occasional movements by stimulation of the mesial surface of the hemisphere in the chimpanzee (*f*, *s*, and *h*, Fig. 4), which they considered different from movements obtained from the "motor areas."

Responses Involving Isolated Muscle Groups: Grünbaum and Sherrington [5] and Leyton and Sherrington [32] were able, in anthropoids, to extend the anterior border of the excitable cortex forward by means of secondary facilitation and to produce effects from the intermediate precentral cortex comparable to those yielded by the motor cortex. The Vogts,[6b] in monkeys, and Foerster,[7] in man, also demonstrated isolated movements from the posterior portion of the intermediate precentral area and pointed out that these responses could be abolished by incision of the cortex between the motor area and the point of stimulation.

Stimulation of Supplementary Motor Area.—The motor responses which we have observed upon stimulation of the supplementary motor area have been obtained at a higher threshold than the other responses, such as vocalization and inhibition of voluntary activity, which characterize this area. The movements of the face and jaw which accompany vocalization (or the arrest of speech) have already been mentioned. These movements were described as pulling of the mouth to the side, twitching of the lower lip, or movements as though the subject were trying to speak. Only twice were the face movements not associated with vocalization or inability to speak. Once there was twitching of the ipsilateral corner of the mouth, together with rotation of the head away from the side of stimulation, and in another patient movement of the jaw was produced.

Twenty-six responses involving arm movement were observed in 10 patients. In all but eight responses the arm movement was part of a complex response involving one or more of the following: leg movement (11 responses), inability to speak (8 responses), eye responses (6 responses), and head movement (2 responses). The movements were most frequently at the elbow and shoulder, although in several instances there were movements of the fingers and hand.

Only three responses, in two patients, were confined to the leg. Two of these were in the same patient and may well have been due to spread of discharge to the adjacent motor leg area, as this patient's attacks began habitually in the contralateral leg. In other cases leg movement was associated with arm movement or with other complexes.

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32. Leyton, A. S. F., and Sherrington, C. S.: Observation of the Excitable Cortex of Chimpanzee, Orangutan, and Gorilla, Quart. J. Exper. Physiol. **11**:135-222, 1917.

It may be that the number of cases in which we have produced movement from the supplementary motor area is not sufficient to justify a final judgment. Tentatively, however, we must consider that there is no well-developed topographic arrangement of representation of the various parts of the body in this area. Nevertheless, on restimulation, the same response may consistently be elicited from a given point, suggesting a constant, patternlike representation of movements and postures.

A description of the distribution of motor responses is not sufficient to convey a picture of these movements. The character of movement is perhaps more important.

The movements which we have produced by stimulation of the supplementary motor area may be divided into three types: (1) assumption of postures; (2) maneuvers, such as stepping, and (3) rapid incoordinate movements. Before these types are considered in detail, it should be emphasized that they are not always clearly separable from each other. For example, a certain stimulation may produce a complex postural adjustment, but it may also induce a rhythmic maneuver. Similarly, a posture or maneuver is frequently accompanied by other responses, such as vocalization, arrest of voluntary activity, or pupillary dilatation.

Assumption of Postures: This kind of movement is slow to develop and seems to reach an end point. One is impressed by the postural end result more than by the action of the parts which go to produce it. Adversive movements, deviation of the eyes, and synergies of the trunk and extremities are seen in various combinations. The movements of the extremities are frequently bilateral.

Most frequently seen is the slow assumption of a posture in which the contralateral arm is abducted and externally rotated at the shoulder and flexed at the elbow. One gains the impression in some cases that the contralteral hand is raised in preparation for its use in a complicated act, and that meanwhile the gaze is directed by movement of head and eyes toward the hand. In the assumption of this posture the musculature of both sides of the body is employed appropriately so as to bring about the change of position. On one occasion we have seen bilateral facial movements produce a fixed puckering of the lips.

It is our impression that many of the postural synergies which result from stimulation of the supplementary motor area would, with more prolonged stimulation, have gone on to become more elaborate and to have approached the full synergic employment of all extremities and the trunk. The stimulating electrode has frequently been removed at the first evidence of response, and thus the opportunity of producing more of the elaborate synergic responses may have been missed. If this surmise is correct, it would be proper to consider many of the motor effects as fractions of an uncompleted complex.

Maneuver: In contrast with the postural response, a maneuver does not slowly approach an end point. Instead, it consists of a definite series of movements in complicated pattern. These movements may be repeated during the application of a single stimulation. Stepping movements, a waving movement of the hand, and fairly complex movements of the hand involving successive flexion and extension of the fingers and wrist have been seen.

As an example, both postures and maneuvers were produced in A. T. (Case 5; Fig. 12). In this patient stimulation at Point *17* caused extension and abduction

of the fingers of the left hand. When this stimulation was repeated, there were flexion of the wrist and extreme extension of the fingers, followed by apposition of the thumb and fingers. This seemed to be a definite maneuver of the hand and could be repeated when the same point was restimulated. When Point *18* was excited, there were flexion of the right knee and extension of the left leg. The left arm became externally rotated. Stimulation of Point *19* caused flexion of the right knee and an external movement of the left foot. At Point *22* stimulation caused extension of the left leg. The right knee flexed three times, and after the third movement remained flexed. The right arm flexed as well. The pupils were dilated, but the patient was able to look at the observer. The eyes did not deviate.

Rapid Incoordinate Movements: This kind of movement is much less frequently elicited than the synergies which have been described. One patient (G. L.) showed a sudden, rapid flexion of the contralateral elbow when a point in the supplementary motor area was stimulated. This response caused him to strike his nose with his hand.

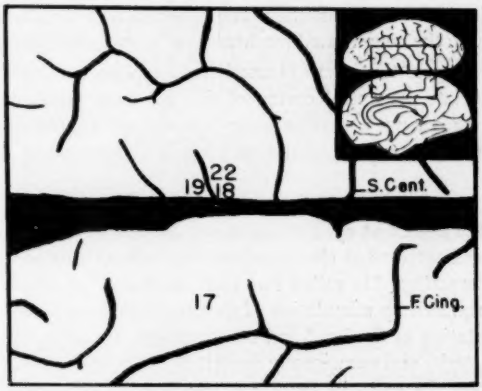

Fig. 12 (Case 5, A. T.).—Points of stimulation on the right hemisphere. These responses were obtained with the Rahm stimulator at 60 cps and 5 volts. The responses are described in the text.

Autonomic Responses

Of the responses that may be called autonomic, pupillary dilation was most frequently observed. Examples of such responses may be found in the legends of Figures *7B* and 12. The pupillary effects were frequently associated with other responses, which have been described. Acceleration of the heart rate was observed twice, and on one occasion the acceleration occurred at the onset of an attack which was produced by the stimulation.

In one patient, stimulation of a point in the supplementary motor area caused arrest of breathing in the position of inspiration, and this lasted almost a full minute.[33]

33. This was one of the few cases in which stimulation was carried out while a record of respiratory movements was being made.

Sensory Responses

Four patients reported sensory experiences upon stimulation of the supplementary motor area. Five responses, in three patients, were described as unlocalized bodily sensations, and this sensation in one of the patients was his own epileptic aura. Such expressions as "a funny feeling all over" and "I felt awful all over" were used by patients to describe these sensations.

Localized sensory responses were elicited in the contralateral leg in two patients, and on one occasion in both legs. One of the contralateral-leg responses was the patient's own aura. Other sensations, which had also been the patient's habitual aura, were: haziness of vision, epigastric sensation, and head sensation.

Recently, a patient reported that during stimulation of the supplementary motor area his extremities felt as though they were paralyzed and he moved them just to make sure that he was able to.

Aphasia

As pointed out above, stimulation of separate areas in the frontal, the parietal, and the temporal cortex of the dominant hemisphere is capable of producing aphasia during the continuance of the stimulus. The application of the electrode thus results in interference with the complicated mechanism of word selection.[34]

Our results suggest that there is another area of speech representation in the superior intermediate precentral cortex of the dominant hemisphere. This representation seems to occupy a narrow zone between the supplementary motor area and the motor area of foot representation (Fig. 1). Analysis of this evidence will be omitted here.

Local Seizures

Turning of the head and eyes and synergic movements of the extremities have been described by Foerster [7] as characteristic of attacks arising in the general region which we are discussing. He called this kind of attack "adversive." Our analysis of 20 seizures produced by stimulation of the supplementary motor cortex indicates that, although rotation of the head and contraversive deviation of gaze form a part of many of the attacks and occasionally constitute the initial event, these movements are far from being the essential feature of the attacks. The most frequent initial sign has, instead, been inhibitory.

Of the 18 attacks produced by stimulation of the mesial intermediate precentral region in 10 patients, seven were initiated by a sensory aura. Twice in this group of seven attacks, epigastric sensation was followed by palpitation, and in one of these episodes the pulse rate rose from 86 to 120 per minute. In another attack the patient complained of a tight feeling in his stomach and chest. There were two instances of nausea and three of head sensation.

The most frequent initial external sign was inability to reply or arrest of speech. After an initial silence, three patients vocalized. In one the vocalization was rhythmic in quality, and in the other two it was steady. Inability to speak, with or without vocalization, was most frequently followed by deviation of gaze or pupillary change, or a combination of these two phenomena. Movements in the contralateral extremities often followed.

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34. Preston Robb [29] has discussed certain aspects of speech representation in our patients. Further analysis of this subject is being carried out by our associate, Dr. Lamar Roberts.

Of the remaining eight attacks, arm movement was the initial external manifestation in five. This arm movement did not resemble that of a Jacksonian motor movement. Deviation of eyes and head initiated one attack, and mouth movements and eye-turning heralded another.

As is the case with focal responses to stimulation, the threshold for eliciting seizures from the supplementary motor area is usually higher than that in the primary motor or sensory cortex.

In one patient, J. P. (Case 6; Fig. 13), stimulation of Point *19* made it impossible for her to respond. At the same time, there was slight dilation of the pupils. An after-discharge was recorded at a nearby electrode. Similarly, when Point *20* was stimulated, she did not respond. The anesthetist lifted her eyelid and found the pupil to be dilated and her eye turned upward. When asked about this, she answered that she did not know why she did not reply. An after-discharge followed removal of the stimulator for about 12 sec. Stimulation at Point *24*

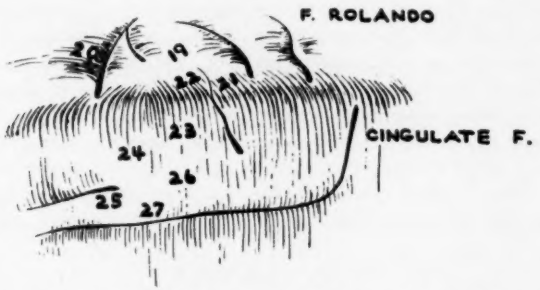

Fig. 13 (Case 6, J. P.), mesial view of the right hemisphere elaborated from a sketch made at the time of operation. The figure is one-half natural size. Responses to stimulation are indicated as follows:

Voltage	Points of Stimulation	Results
2	19	Patient did not respond. There was slight dilation of the pupils. After-discharge was recorded from a nearby electrode.
	20	Patient did not respond. Dr. Pasquet opened the lids and found the pupils dilated and the eyes turned upward. When asked afterward why she did not reply, she said she did not know. There was electrographic after-discharge.
	21	Flexion of the left knee.
	22	Stimulation was continued while the patient was repeatedly asked to reply. There was no reply. The pupils dilated. Afterward, in explanation, she said she "couldn't get it out."
	23	When this point was stimulated, she was unable to reply. The moment stimulation was stopped, she said, "Nothing." Stimulation at Point 23 was repeated while the patient was counting. Arrest of counting was instantaneous when the stimulus was applied. When asked if this were like some of her attacks, she said, "Yes, I stopped talking."
	24	Stimulation at Point 24 produced a short seizure consisting of extension of the fingers of the left hand, supination of the arm, and dilation of the pupils. This stopped immediately upon cessation of stimulation, and the patient then continued the counting which had been stopped.
	22	Stimulation was repeated while the patient was counting. She slowed down but did not stop.
	25	There were extension of the fingers of the left hand, extension of the arm, and dilation of the pupils. There was no after-discharge.
3	24	Stimulation was repeated while the patient was counting. Counting stopped after two additional numbers had been recited. There was movement of the left arm, which stopped as soon as stimulation was withdrawn.
	26	There were movement of the left arm and turning of the head to the left, raising of the trunk off the table, dilation of the pupils, and deviation of eyes to the left. This continued for 2 sec. after stimulation, and she said then that she had had an attack. This stimulation was then repeated, after the patient was asked to let the operator know if she had an aura. The previous seizure was duplicated, and afterward the patient stated that she had felt something in her head—like the sensation before an attack.
	22	This point was restimulated while the patient was counting. She stopped and after an interval began again where she had left off.
	27	A seizure similar to that evoked from Point 26 was produced.

produced a short seizure, characterized by extension of the fingers of the left hand, supination of the arm, and dilation of the pupils. This stopped immediately, however, when stimulation was withdrawn, and the patient was then able to resume counting. At Point *26* stimulation resulted in movement of the left arm and rotation of the head to the left, movement of the trunk, and dilation of the pupil with deviation of the eyes. This continued for two seconds after the withdrawal of the electrodes. Seizures similar to the last one were obtained again at Point *26* and also at Point *27*, and the patient stated in each case that it was preceded by a head sensation.

It is clear that, as one would predict from the results of focal stimulation of the supplementary motor area, the seizures which arise spontaneously here are both complex and variable. It is only partially descriptive to characterize them as "adversive" attacks.

Comment

We have described the results of stimulation and of epileptic discharge in a zone anterior to the upper part of the somatic motor strip of the cerebral cortex of man. These results have been discussed under the following headings: vocalization, alteration of voluntary activity, movements of the extremities and body, autonomic responses, sensory responses, and aphasia. Although the motor effects of stimulation sometimes include turning and looking to the opposite side, the term "adversive" [35] does not in any way cover the majority of responses. The area from which results were obtained is well circumscribed and is situated largely on the mesial aspect of the first frontal convolution (Fig. 1). Only rarely were such responses obtained from the external surface, and then only very close to the longitudinal sinus.[36]

It is evident that these responses to stimulation are sensory, as well as motor, but taken together they are predominantly motor. The motor effect may be that of movement or that of inhibition of movement. We would propose the noncommittal term "supplementary motor area," or, to be more exact, supplementary motor-and-sensory area.

Comparison of the responses from the supplementary motor area with those obtained by stimulation of the precentral gyrus shows similarities and differences. The responses from the precentral gyrus are predominantly motor also, but there is an invariable topographic representation of parts of the opposite side of the body, laid down in a fixed order. Movement in the pre-Rolandic strip is contralateral, never bilateral, except in regard to those parts of the body which are not divisible into two parts, such as the tongue and throat.

In the supplementary motor area in man, on the other hand, there seems to be no such topographic representation. The postures assumed and the rhythmic movements produced are made possible by employment of ipsilateral limbs and body parts, as well as the contralateral parts. The supplementary motor area has control

35. The term "frontal adversive-field," employed by Foerster, apparently referred to the lateral aspect of the hemisphere, rather than to the mesial surface.

36. It should be added here that, since the first draft of this study was undertaken, two years ago, opportunity has been presented on several occasions to stimulate the mesial surface of the parietal lobe within the longitudinal fissure, with positive results. It seems possible that in man the supplementary area as a functional motor unit may extend around into a position posterior to the Rolandic motor foot area. Stimulation in this posterior position has also produced sensation in all four extremities. Verification and amplification of this suggestion must await the fortunate chance of clinical exploration.

over the musculature of both sides of the body, although the pattern of movement brought about by stimulation of the right side may be the opposite of that produced by stimulation of the left. For example, if turning movements are produced, both legs and arms may be moved, but the turning movement is away from the side stimulated. The turning is likely to be the assumption of a posture, rather than continued rotation.

Vocalization produced in the pre-Rolandic motor strip resembles that which results from stimulation of the supplementary motor area, except that the latter may oftener be rhythmic. Sensation when produced in the supplementary motor area is quite different from that resulting from stimulation of the precentral or the postcentral gyrus. It is likely to be bilateral and diffuse and sometimes seems to be referred to certain viscera.

It is interesting, also, to compare the Rolandic motor and the supplementary motor areas with respect to the kinds of inhibitory effects which can be produced from each. Stimulation of the precentral hand area may interfere with voluntary use of the hand even, in some cases, when no hand movement is produced. But it does not inhibit movement of the other hand or the legs. On the other hand, stimulation of an inhibitory point in the supplementary motor area and, as we have recently observed, stimulation of a "speech-arrest" point in the lower Rolandic region produce similar effects in that the subject's ability to speak or to move his fingers is alike impaired.

Topographically, the supplementary motor area lies largely within the sagittal fissure anterior to the primary (Rolandic) motor leg representation. In the dominant hemisphere there seems to be a narrow strip of cortex between the two which is devoted to speech representation.

The functional relationship between the supplementary motor area and the Rolandic motor region is not nearly so clearly defined. The Vogts [6b] established in monkeys that isolated motor responses from stimulation of Area 6a depended upon the presence of an intact Area 4 and that these responses could be abolished by incision in the cortex between the two areas. A similar situation in man was described by Foerster.[7] Complex adversive responses were not abolished, however, in man or monkey by incision of the cortex in this fashion.

In our experience, opportunity to stimulate the mesial surface of the hemisphere in the vicinity of the supplementary motor area, in the absence of the precentral convolution, has presented itself in three cases. In one case only slowing of speech could be elicited. In a second case (A. A.), at a previous operation, the arm and face sub-division of the precentral and postcentral gyri had been excised on the right side. The second operation was carried out on the same side three months after the first. At this time stimulation of a zone on the mesial surface of the first frontal convolution 3.5 cm. anterior to the upper extremity of the central sulcus caused arrest of counting, movements of the contralateral (left) leg and arm, rotation of the head toward the left, eye movements, and pupillary dilation.

In the third case (B. L.) a vascular occlusion in the right hemisphere in 1942 had left the patient with severe hemiplegia and a causalgia-like pain on the left side, especially in the axilla and the chest wall. At his first operation, five years after the onset of his illness, the right postcentral gyrus was excised. His pain was relieved for 18 mo., but recurred. At the time of his second operation, two and one-half years after the postcentral gyrus had been excised, it was possible to reproduce his pain by stimulation of the precentral gyrus; accordingly, the useless precentral gyrus was removed completely. Immediately after the excision had been made, stimulation of the supplementary motor area was carried out. At various points

stimulation resulted in vocalization of meaningless, but quite complicated, syllables. Movements of the contralateral (paralyzed) arm were produced from the supplementary motor area, as was arrest of movements of the fingers on the right (ipsilateral) side.

One may conclude, therefore, that the Rolandic motor area plays no essential role in the production of these responses from the supplementary motor area.

There is a striking resemblance between the results of stimulation of the supplementary motor area in man and the results that have been reported from stimulation of the anterior cingulate cortex of monkeys. Smith [37] described vocalization, inhibition of spontaneous movements, pupillary effects, and complex motor responses produced by stimulation of the anterior cingulate region. These results have been confirmed by Ward [38] and extended by Kaada, Pribram, and Epstein.[39] This similarity deserves consideration and discussion.

The physical spread of current from the intermediate precentral to the cingulate cortex is unthinkable because of the distances involved in the human brain (some of the responses have come from the convexity) and because of the weakness of the currents used. Indeed, our stimulation points were closer to the primary motor area than to the cingulate gyrus in many instances, and yet there was no spread of current to it and no leg movements, as there might have been if spread of current were a factor.

In a considerable number of cases we stimulated the cingulate gyrus in the vicinity of the supplementary motor area, without producing observable effects. Stimulation farther anterior and inferior upon the cingulate gyrus does produce respiratory effects in man, but this is another consideration, to be dealt with elsewhere. Our present conclusion is that the supplementary motor area in man does not cross the cingulate fissure. It does, however, extend into this fissure on its superior bank.

SUMMARY

1. In a relatively small zone of each hemisphere, anterior to the motor area for the lower extremity, there exists an area which yields characteristic responses to stimulation. This area, which we have called the supplementary motor area, is situated almost altogether within the median longitudinal fissure and anterior to the primary motor foot area.[36]

2. The threshold for stimulation of a supplementary motor area in both human subjects and monkeys is a little higher than that for the precentral and postcentral regions, and yet the effect is clearly not due to spread of excitation across the cortex to those regions.

3. The results of experimental studies in monkeys are as follows:

(*a*) Stimulation of this region has revealed a motor representation of the contralateral extremities. There is a definite topographic organization which it has not

37. Smith, W. K.: Vocalization and Other Responses Elicited by Excitation of the Regio Cingularis in the Monkey, Am. J. Physiol. **133**:451-462 (June) 1941; The Functional Significance of the Rostral Cingular Cortex as Revealed by Its Responses to Electrical Excitation, J. Neurophysiol. **8**:241-255 (May) 1945.

38. Ward, A. A.: The Cingular Gyrus: Area 24, J. Neurophysiol. **11**:13-23 (Jan.) 1948.

39. Kaada, B. R.; Pribram, K. H., and Epstein, J. A.: Respiratory and Vascular Responses in Monkeys from Temporal Pole, Insula, Orbital Surface and Cingulate Gyrus, J. Neurophysiol. **12**:347-356 (Sept.) 1949.

been possible to reproduce in man, perhaps owing to the conditions imposed upon clinical exploration.

(*b*) Inhibition of spontaneous grasping in the opposite hand has been produced by stimulation of the supplementary motor area, and removal of the area has resulted in forced (or "reflex") grasping. Reflex grasping is a specific sign of removal of this particular cortical area in the monkey.

4. In man the results of cortical stimulation are as follows:

(*a*) Vocalization, of a more variable and complex character than that elicited from the lower Rolandic cortex, results from stimulation here.

(*b*) Inhibition of voluntary activity (the test situation was oftenest speech) has been the most frequent effect of stimulation of this area. The patients' descriptions indicate that, although conscious, they were unable to carry out or to continue the prescribed activity.

(*c*) Synergies resulting in the assumption of characteristic postures and in the performance of complex maneuvers have been produced by stimulation of the supplementary motor area.

(*d*) Pupillary dilation and, less often, cardioacceleration have been observed. On one occasion arrest of breathing was recorded.

(*e*) A few sensory experiences have been produced, usually a general bodily sensation or one related to viscera.

(*f*) Excision of the supplementary motor area has produced no permanent deficit in maintenance of posture or capacity for movement.

(*g*) Local seizures may be produced by stimulation in this region. These attacks may be considerably more complicated in pattern than simple turning to the opposite side.

(*h*) In general, the supplementary motor area differs from the pre-Rolandic motor area in that stimulation has an effect upon the limbs of the ipsilateral, as well as the contralateral, side of the body.

(*i*) Although each supplementary motor area may exert some motor influence upon all four extremities and the trunk in the maintenance of postures and the carrying out of maneuvers, the most frequent motor effect of each is to produce contraversion and movement of the contralateral arm.

ANTIDEPRESSIVE ACTION OF 5-(1,3-DIMETHYLBUTYL)-5-ETHYLBARBITURIC ACID

JACQUES S. GOTTLIEB, M.D.
IOWA CITY

AMOBARBITAL SODIUM

AMOBARBITAL (amytal®) sodium (sodium isoamylethyl barbiturate), since the report of Lindemann,[1] in 1931, has been known to have a temporary ameliorating effect upon the symptoms of patients with depression. This drug when administered intravenously in subnarcotic doses usually produces a reaction in which the symptoms lessen in severity and the patient more closely approaches his normal. The commoner response is for the depression partially to subside, the patient feeling more comfortable, pleasant, alert, and even on occasion euphoric. Less often the depression is felt more strongly and expressed more overtly. In addition to these shifts in mood, other changes may become apparent. There may be an increase in the speed of retarded mental processes. The desire to communicate personal problems and experiences may improve. Patients who are agitated may become quiet; those who are retarded may move with greater ease. There may be a diminution of anxiety and tension. Even the self-abasing and derogatory thoughts, the hopeless feelings, and suicidal impulses may no longer be overwhelming, and even on occasion may subside completely.

All patients, however, do not have the same order of response; there is considerable individual variability. About 90% of those who have not been on daily sedation show some degree of improvement; the remainder fail to respond.[2]

AMPHETAMINE SULFATE

Amphetamine sulfate (benzedrine® sulfate) likewise is an effective antidepressant.[3] In normal subjects and in many fatigue states due to various causes there develop frequently an increased feeling of alertness, a sense of well-being,

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From the Iowa Psychopathic Hospital and the State University of Iowa College of Medicine.
This is the seventh paper in a series of psychopharmacologic studies of schizophrenia and depression.
Dr. Gordon A. Alles, Pasadena, Calif., prepared and furnished the experimental drug for this clinical study.

1. Lindemann, E.: The Psychopathological Effect of Sodium Amytal, Proc. Soc. Exper. Biol. & Med. **28**:864, 1931; Psychological Changes in Normal and Abnormal Individuals Under the Influence of Sodium Amytal, Am. J. Psychiat. **11**:1083, 1932.

2. Gottlieb, J. S.: Unpublished data.

3. Myerson, A.: Effect of Benzedrine Sulfate on Mood and Fatigue in Normal and in Neurotic Persons, Arch. Neurol. & Psychiat. **36**:816 (Oct.) 1936. Nathanson, M. H.: New Adrenalin-Like Compounds: Their Action and Therapeutic Application, Calif. & West. Med. **57**:301, 1942. Reifenstein, E. C., Jr., and Davidoff, E.: Psychological Effects of Benzedrine Sulfate, Am. J. Psychol. **52**:56, 1939.

and an increase in energy, with an overcoming of fatigue. Mild euphoria on occasion develops. In patients with pathologic depression, however, this drug has but mild effects upon the mood.[4]

Combination of Amobarbital Sodium and Amphetamine Sulfate.—When the two drugs, amobarbital sodium and amphetamine sulfate, are given in combination, a synergistic effect occurs.[5] One such advantage of this combination is the analeptic effect of the amphetamine sulfate. By its addition the hypnotic effect of the amobarbital sodium is reduced; that is, drowsiness is diminished, and the clinical response to amobarbital sodium becomes more apparent. A second advantage is the increase in the duration of the clinical response produced by amobarbital sodium, from an average of two and one-half hours with amobarbital alone, to five and one-half hours with the combination. It should be noted that the better clinical response is obtained when the amphetamine sulfate is administered either with or immediately after the amobarbital sodium. In addition, when both drugs are administered daily, patients with depression are able to respond with approximately a similar reaction each day both in the degree of clinical improvement and in the duration.[6]

These observations led to the use of amobarbital sodium and amphetamine sulfate in the symptomatic treatment of patients with depression.[7] Symptomatic improvement allowed many patients whose illnesses were mild to continue their tasks while receiving psychotherapy. Other patients with short depressive episodes could be relieved sufficiently to continue their daily responsibilities until their illnesses subsided. Even those patients with severe depression experienced varying degrees of improvement; a small number of them (23%) recovered while awaiting hospitalization.

The use of amobarbital sodium and amphetamine sulfate in the symptomatic treatment of patients with depression, however, is limited. A significant number of such patients do not respond adequately to the medication; some do not respond at all, others but poorly. In other patients, although the response may be good, the duration is short. One other limitation is a gradual diminution in the intensity of the responses in some patients after prolonged daily repetition of the drugs.

STATEMENT OF THE PROBLEM

These limitations posed the question whether other drugs related to either of these two, amobarbital sodium or amphetamine sulfate, may be more effective as antidepressive or euphorogenic agents, and thus be more useful clinically.

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4. Dub, L. A., and Lurie, L. A.: Use of Benzedrine in the Depressed Phase of the Psychotic State, Ohio M. J. **35**:39, 1939. Watts, C. A. H.: Endogenous Depression in General Practice, Brit. M. J. **1**:11, 1947. Gottlieb, J. S.: Unpublished observations.

5. Myerson, A.: The Reciprocal Pharmacological Effects of Amphetamine (Benzedrine) Sulfate and the Barbiturates, New England J. Med. **221**:561, 1939. Gottlieb, J. S., and Coburn, F. E.: Psychopharmacologic Study of Schizophrenia and Depressions: Intravenous Administration of Sodium Amytal and Amphetamine Sulfate Separately and in Various Combinations, Arch. Neurol. & Psychiat. **51**:260 (March) 1944.

6. Gottlieb, J. S.; Krouse, H., and Freidinger, A. W.: Psychopharmacologic Study of Schizophrenia and Depressions: Comparison of Tolerance to Sodium Amytal and Amphetamine Sulfate, Arch. Neurol. & Psychiat. **54**:372 (Nov.-Dec.) 1945.

7. Gottlieb, J. S.: The Use of Sodium Amytal and Benzedrine Sulfate in the Symptomatic Treatment of Depressions, Dis. Nerv. System **10**:50, 1949.

Amphetamine (1-methylphenethylamine) is a sympathomimetic amine, one of a series of drugs which resemble ephedrine in a number of respects. Amphetamine, however, is one of the most potent stimulants of the central nervous system of all the known sympathomimetic drugs.[8] Other drugs in this series, such as *d*-desoxyephedrine (pervitin®),[9] and *d*-amphetamine (dexedrine® sulfate),[10] have been compared to amphetamine in action. The probabilities of finding another drug in the sympathomimetic amine series having a significantly greater euphorogenic effect than those already studied is pharmacologically not great.

On the other hand, amobarbital sodium, the sodium salt of 5-ethyl-5-isoamylbarbituratic acid, is one of a large series of related compounds called barbiturates.[8] Although several hundred barbiturates have been prepared, only a relatively few have been adequately studied pharmacologically. The clinically useful barbiturates have been those with hypnotic effects. However, as the chemical structure is changed, there is a corresponding change in pharmacologic action. The majority of known barbiturates do not have a hypnotic action but are stimulants of the central nervous system and have convulsive properties. As the alkyl carbon chain increases in length, there is a decrease in hypnotic potency, with a corresponding increase in convulsive action. Thus, amobarbital sodium, with four carbon atoms in its side chain, has a shorter action than barbital, with two. As the carbon atoms in the side chain increase to over five or six, only convulsive properties are present. Alkyl groups attached to both the nitrogen atoms also tend to produce convulsant compounds. Many of these stimulating or convulsion-producing barbiturates have not yet been studied in man.

Amobarbital sodium, when given in subnarcotic amounts, produces an increase in the beta activity of the electrocortical potentials.[11] With the development of the narcotic state, the rapid electroencephalographic activity disappears. Since the antidepressant effect of amobarbital sodium occurs when the drug is given in subnarcotic amounts, it appeared possible that this desired effect might be due to the stimulation of the neural axis, which was subsequently masked by the predominant hypnotic action of the drug. It was decided, therefore, to study the effects of a convulsant barbiturate on patients with depression to determine whether or not any euphorogenic effect would result.

THE EXPERIMENTAL DRUG

The convulsant barbiturate chosen for study was 5-(1,3-dimethylbutyl)-5-ethylbarbituric acid. The chemical formula of this drug is presented in the accompanying figure, where it may be compared with the formulas for barbital and amobarbital

8. Goodman, L., and Gilman, A.: The Pharmacological Basis of Therapeutics, New York, The Macmillan Company, 1941.

9. Levine, J.; Rinkel, M., and Greenblatt, M.: Pervitin® in Neuropsychiatry: Comparison with Sodium Amytal and Amphetamine Sulfate, Arch. Neurol. & Psychiat. **63**:351 (Feb.) 1950.

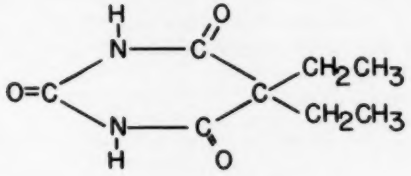
10. Davidoff, E.: A Comparison of the Stimulating Effect of Amphetamine Dextroamphetamine and Dextro-*N*-Methyl Amphetamine (Dextro-Desoxyephedrine), M. Rec. **156**:422, 1943.

11. Brazier, M. A. B., and Finesinger, J. E.: Action of Barbiturates on the Cerebral Cortex: Electroencephalographic Studies, Arch. Neurol. & Psychiat. **53**:51 (Jan.) 1945. Gottlieb, J. S.; Knott, J. R., and Kimble, L. L.: Psychopharmacologic Study of Schizophrenia and Depression: The Influence of Electric Convulsive Therapy on the Sodium Amytal Response of the Electroencephalogram, Am. J. Psychiat. **104**:686, 1948.

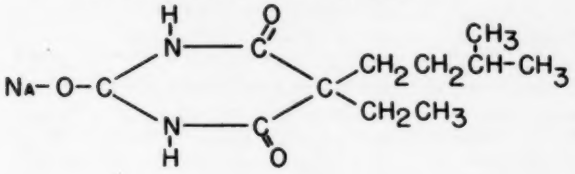
sodium (amytal® sodium). It should be noted that the experimental drug closely resembles amobarbital sodium in formula, with the same number of carbon atoms in the side chains, but with a dimethylbutyl component substituted for the amylethyl one.

This experimental drug was first reported by Shonle, Waldo, Keltch, and Coles,[12] who indicated that it produced convulsions in rats and had no hypnotic or anesthetic effect in sublethal doses. Knoefel[13] studied this compound further in

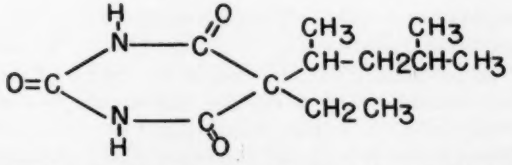
BARBITAL
(DIETHYLBARBITURIC ACID)



SODIUM AMYTAL®
(SODIUM ISOAMYLETHYLBARBITURATE)



5-(1,3-DIMETHYLBUTYL)-5-ETHYLBARBITURIC ACID



Formulas for barbital, amobarbital (amytal®) sodium, and the experimental drug, 5-(1,3-dimethylbutyl)-5-ethylbarbituric acid. Note that the last compound closely resembles amobarbital sodium by having the same number of carbon atoms in the side chains, but differs by the presence of a dimethylbutyl component, rather than an amylethyl one.

12. Shonle, H. A.; Waldo, J. H.; Keltch, A. K., and Coles, H. W.: Relation of the Structure of Dialkyl Barbituric Acids to the Length of Their Action, J. Am. Chem. Soc. **58**:585, 1936.

13. Knoefel, P. K.: The Action of a Convulsant Barbiturate, J. Pharmacol. & Exper. Therap. **57**:130, 1936; Stimulation and Depression of the Central Nervous System by Derivatives of Barbituric and Thiobarbituric Acids, ibid. **84**:26, 1945.

animals and compared its action with those of caffeine, picrotoxin, and strychnine. In comparative experiments on the production of flexion and crossed-extension reflexes, this barbiturate was rated as more active than caffeine, about one-fourth as active as picrotoxin, and one two-hundred-and-fiftieth as active as strychnine. This comparison should not lead to the conclusion that the over-all effect on the central nervous system of the experimental drug is described by these particular experiments. It is difficult to conduct pharmacological studies in animals to obtain any indication of the effects of a drug upon any aspect of affectivity. It is only in man that the effect of drugs on emotion can be adequately determined.

This experimental barbiturate is not as effective as an analeptic as are some other drugs which stimulate the central nervous system. A fatal outcome with a uniformly fatal dose of pentobarbital in rabbits was not prevented. On the other hand, the acute lethal dose of this experimental barbiturate is raised by the administration of amobarbital.[13]

Summary of Reactions with the Sodium Salt of 5-(1,3-Dimethylbutyl)-5-Ethylbarbituric Acid.

				Duration of Illness,		Response				Toxic Symptoms				Effective Dose,
Case	Diagnosis*	Age	Sex	Mo.	Severity of Illness	Very Good	Moderate	Slight	None	Itching; Perspiration	Flush	Cyanosis	Duration of Response†	Mg.
1	MDD	47	M	12	Severe	+++	....	..	..	.....	.....	.....	D	50 100
2	MDD	44	M	12	Severe	+++	....	..	..	.....	.....	.....	D & f. m.	100
3	MDD	54	M	1	Severe	.....	++	..	..	.....	.....	.....	D	100
4	MDD	52	F	12	Moderate	.....	....	..	0	++	Nausea	Vomiting	..	100
5	IPM	54	M	3	Severe	.....	....	..	0	+	.....	.....	..	100
6	IPM	69	F	3	Severe	.....	++	..	..	.....	.....	.....	D	100 150
7	MDD	52	M	1	Mild	+++	....	..	..	+++	Dizziness	Ataxia	D	100
8	MDD	35	M	2	Moderate	.....	....	?	0	++	Shaking	Paresthesias	..	50 100
9	MDD	43	F	12	Severe	.....	....	..	0	+++	Punctate rash		..	100
10	SeP	24	F	6	Severe	+++	....	..	..	.....	++	++	D & f. m.	100 50

* MDD indicates manic-depressive psychosis, depressive type; IPM, involutional psychosis, melancholia, and SeP, paranoid type of schizophrenia.

† D indicates "throughout day"; and D & f. m., "throughout day and following morning."

Swanson and Chen [14] indicated that the convulsant dose (CD_{50}) is about 10 mg. per kilogram, given subcutaneously or intraperitoneally, for mice and rats and about 2 mg. per kilogram, given intravenously, for the guinea pig, rabbit, cat, dog, and monkey. However, it is to be expected that stimulating effects on the central nervous system at doses lower than those required to produce convulsions may be exhibited. Hence it was thought that the subconvulsant stimulating effects of this drug could be studied in patients with depression by maintaining the dosage safely below the convulsive level.

OBSERVATIONS

Ten patients were given the sodium salt of 5-(1,3-dimethylbutyl)-5-ethylbarbituric acid by mouth in doses of from 50 to 150 mg. Of these 10 patients, seven were ill with manic-depressive psychosis, depressive type; two, with involutional

14. Swanson, E. E., and Chen, K. K.: The Aberrant Action of Sodium 1:3-Dimethylbutyl-ethyl-Barbiturate, Quart. J. Pharm. & Pharmacol. **12**:657, 1939.

psychosis, melancholia, and one, with schizophrenia, paranoid type, but with considerable depressive coloring. The protocols for the responses of these patients to this drug appear in the appendix. Some of the observations are summarized in the accompanying table. Inspection of this table and a review of the protocols reveal the following facts:

1. The drug had an antidepressive or euphorogenic effect in six of the 10 patients. The response to the drug of four of these patients was considered "very good"; that is, the patients either returned to a normal affective state, with disappearance of the symptoms and signs of their illness, or became euphoric. Two patients responded with considerable improvement, but there was not complete disappearance of symptoms. No hypnotic action of the drug was apparent, although these patients could now sleep in a normal way at night. 2. The responses to the morning administration of the drug persisted throughout the day and into the evening or the following morning. The duration of response was thus rather long as compared with the average duration for amobarbital sodium (two and one-half hours) or amobarbital sodium combined with amphetamine sulfate (five and a half hours). 3. From an hour to an hour and a half was required before any clinical change was detectable. 4. Four patients did not have any change in their disease symptoms. 5. These four patients, and two others, exhibited undesirable effects. The commonest manifestation was intense itching of the skin, associated usually with perspiration and, on one occasion, a fine, punctate rash. In addition, there were flushing in four instances and mild cyanosis on one occasion. Other undesirable symptoms were nausea and vomiting, in one patient; vertigo and ataxia, in another; tremors and paresthesias, in a third, and a reaction which suggested an abortive seizure, in a fourth. This patient experienced a sudden change in behavior about five hours after taking the drug, when she became confused, incoordinated, incoherent, and flushed. The reaction lasted about 20 minutes. None of these undesirable symptoms were significantly affected by the administration of antihistaminic drugs.

COMMENT

The sodium salt of 5-(1,3-dimethylbutyl)-5-ethylbarbituric acid, a stimulating barbiturate with no hypnotic effect, has powerful antidepressive and euphorogenic effects in certain patients with depression. The frequency and severity of undesirable or toxic manifestations preclude the use of this drug for therapeutic purposes. These experiences with the drug, however, are important, for the following reasons:

1. Since the drug is only one of a number of stimulating barbiturates, it may be that other, closely related compounds may have a similar action without the toxic complications. It would thus appear that study of the actions of other stimulating barbiturates in patients with depression is warranted.

2. The antidepressive effect of this stimulating barbiturate has important theoretical implications. As previously mentioned, amobarbital sodium, when given in subnarcotic amounts, produces an increase in the beta activity of the electrical potentials of the brain.[11] This suggests that this barbiturate has a stimulating action on the central nervous system, which is masked by the hypnotic effect when larger amounts are given. Since the action of 5-(1,3-dimethylbutyl)-5-ethylbarbituric acid is that of a stimulant and its effect is to relieve depression, it follows that it may be the stimulating action, rather than the hypnotic action, of amobarbital sodium that is responsible for its euphorogenic effect.

If it is the stimulating action of barbiturates which produces an antidepressive response in patients with pathologic depression, it is probable, then, that the neural pathophysiology in this disorder is one of hypofunction of some neural area. Furthermore, if the locus of action of barbiturates were known, that area would be implicated as a component of the physiologic malfunctioning in these disorders. Unfortunately, the locus of action of the barbiturates is not definitely known, in spite of a voluminous literature. Study of the deposition of barbiturates in various parts of the brain is inconclusive.[15] The present consensus, based on the observations of numerous investigators, seems to be that the barbiturates act more or less selectively on the hypothalamic functions.[16] More direct evidence is obtained when the effects of a barbiturate on the electroencephalograms of the thalamus, corpus striatum, and cortex in human beings are studied.[17] The earliest changes detected as a response to secobarbital sodium (seconal® sodium; sodium 5-alkyl-5-[1-methylbutyl]-barbiturate), the barbiturate used, are in the thalamus and corpus striatum, the comparable cortical changes lagging behind by four to nine minutes. The electroencephalographic characteristics of the response to the drug are similar to those produced by natural sleep. The implications of this study would suggest that the fundamental locus of action for barbiturates and that for sleep are closely related and that, wherever this locus may be, it dominates the thalamus, the corpus striatum, and the cortex. That the pathophysiology of depression may be closely related to the neural function for sleep is also suggested by the characteristic sleep disturbance of depressed patients, as observed clinically and electroencephalographically.[18] Further studies on animals and man oriented toward the elucidation of the locus of action of barbiturates and their relation to the neural physiology of sleep may assist in clarifying the pathophysiology of depression.

SUMMARY

The problem was to determine whether a barbiturate whose action was primarily that of stimulation of the central nervous system had an antidepressive or a euphorogenic effect in patients with pathologic depression. The stimulating

15. Keeser, E., and Keeser, J.: Über die Lokalization des Veronals, der Phenyläthyl- und Diallylbarbitursäure im Gehirn. (Beitrag zum Schlafproblem), Arch. exper. Path. u. Pharmakol. **125**:251, 1927. Kopanyi, T.; Dille, J. M., and Krop, S.: Studies on Barbiturates: VIII. Distribution of Barbiturates in the Brain, J. Pharmacol. & Exper. Therap. **52**:121, 1934.

16. Leiter, L., and Grinker, R. R.: Role of the Hypothalamus in Regulation of Blood Pressure: Experimental Studies, with Observation on Respiration, Arch. Neurol. & Psychiat. **31**:54 (Jan.) 1934. Masserman, J. H.: Destruction of Hypothalamus in Cats: Effects on Activity of the Central Nervous System and Its Reaction to Sodium Amytal. ibid. **39**:1250 (June) 1938; Effects of Sodium Amytal and Other Drugs on Reactivity of the Hypothalamus of the Cat, ibid. **37**:617 (March) 1937. Feitelberg, S.; Pick, E. P., and von Warsberg, A.: Über centrale Wärme-Erzeugung und Hemmung durch aromatische Amine und Acetylcholin, Arch. internat. pharmacodyn. **61**:447, 1939. Laidlaw, R. E., and Kennard, M. A.: Effects of Anesthesia on the Blood Supply to the Hypothalamus, Am. J. Physiol. **129**:650, 1940.

17. Knott, J. R.; Hayne, R., and Meyers, H. R.: Physiology of Sleep: Wave Characteristics and Temporal Relations of Human Electroencephalograms Simultaneously Recorded from the Thalamus, the Corpus Striatum and the Surface of the Scalp, Arch. Neurol. & Psychiat. **63**:526 (March) 1950.

18. Diaz-Guerrero, R.; Gottlieb, J. S., and Knott, J. R.: The Sleep of Patients with Manic-Depressive Psychosis, Depressive Type: An Electroencephalographic Study, Psychosom. Med. **8**:399, 1946.

barbiturate chosen for study was the sodium salt of 5-(1,3-dimethylbutyl)-5-ethylbarbituric acid. This drug was given in doses of 50 to 150 mg. by mouth to 10 patients who were severely depressed.

1. Four of the 10 patients responded with temporary disappearance of the symptoms and signs of depression or became euphoric. Two other patients responded with considerable improvement of their mood. The remaining four patients failed to respond.

2. The antidepressive response to the drug began between one and one and a half hours after its administration. The duration of the response persisted throughout the day and into the evening or the following morning.

3. The drug produced undesirable side actions in six patients. The commonest manifestation was intense itching and flushing of the skin, with considerable perspiration. In addition, there occurred on occasion a fine punctate rash, cyanosis, nausea and vomiting, vertigo and ataxia, tremors and paresthesias, and a probable abortive seizure.

The undesirable side actions preclude the further study of this drug, but its antidepressive and euphorogenic action suggests that other, closely related stimulating barbiturates may be worthy of study.

APPENDIX

The sodium salt of 5-(1,3-dimethylbutyl)-5-ethylbarbituric acid was given by mouth to 10 patients, whose protocols follow:

CASE 1.—A man aged 47 had an illness of one-year's duration, characterized by severe depression, psychomotor retardation, insomnia, anorexia, loss of weight, numerous somatic complaints, self-blame, suicidal thoughts, and hopeless feelings. He had had a previous similar period of depression at the age of 43.

The diagnosis was manic-depressive psychosis, depressive type.

Feb. 25, 1949: 9 a. m.: He was given 50 mg. of the drug.

10:30 a. m.: The patient noticed a decrease in his feelings of depression.

11:30 a. m.: The patient was less depressed, more talkative, less seclusive, and more friendly. His somatic complaints and self-blame were reduced.

9 p. m.: The condition continued. He slept well.

Feb. 26: 9 a. m.: A 100-mg. dose was given.

10:30 a. m.: The patient was cheerful and friendly, with loss of most of his symptoms of depression. The condition continued until bedtime, at 9 p. m. He slept well.

CASE 2.—A man aged 44 had an illness of one-year's duration, characterized by severe depression and psychomotor retardation. In addition, he suffered from anorexia, loss of weight, insomnia, self-blame, and suicidal thoughts.

The diagnosis was manic-depressive psychosis, depressive type.

March 5, 1949: 9 a. m.: A 100-mg. dose was administered. He was very depressed and withdrawn.

10 a. m.: The patient continued to be very depressed.

11 a. m.: He was more talkative and friendly.

2 p. m.: Improvement continued. Depression and other symptoms were less severe.

5 p. m.: The patient became socially aggressive, talking freely and continuously. His mood was mildly euphoric. Both objectively and subjectively, the patient was greatly improved.

9 p. m.: The patient's condition continued. He slept well.

March 6: 8 a. m.: The patient continued to be more relaxed, talkative, and friendly.

11 a. m.: The patient again became depressed, retarded, and withdrawn.

CASE 3.—A man aged 54, with an illness of one-month's duration, appeared severely depressed and retarded. He felt unworthy, forsaken, and hopeless and was suicidal. He suffered from anorexia and insomnia.

The patient had had one previous similar illness.

The diagnosis was manic-depressive psychosis, depressive type.

April 25, 1949: 10:30 a. m.: A 100-mg. dose was administered. The patient was very depressed, agitated, and frightened, thinking he was to be killed.

11:30 a. m.: He was quieter and more cooperative but still very depressed.

12:00 noon: The patient ate voraciously. He asked to attend to his toilet and groom himself. He conversed with others more freely.

5:00 p. m.: His state continued much the same.

8:00 p. m.: He was more depressed, retarded and withdrawn.

2:00 a. m.: The patient awakened very depressed, agitated, and frightened again.

CASE 4.—A woman aged 52, whose illness had been present for approximately a year, appeared depressed, apprehensive, and irritable and had many somatic complaints. At another hospital, for the present illness, she had received a total of 21 electric convulsions and 25 insulin comas, without significant improvement. She had had three previous depressions, the first occurring at the age of 19.

The diagnosis was manic-depressive psychosis, depressive type.

May 14, 1949: 7:00 a. m.: A 100-mg. dose was given.

7:15 a. m.: The patient began to complain of itching of the hands, feet, and face.

8:00 a. m.: She was scratching and complaining bitterly of intense itching. There were no objective changes in the skin.

8:15 a. m.: Diphenhydramine (benadryl®) hydrochloride, 100 mg., was given.

8:30 a. m.: Nausea and vomiting were present.

9:00 a. m.: Itching diminished. No change in symptoms occurred during the remainder of the day except for sleepiness. There was no improvement of mood.

CASE 5.—A man aged 54 was admitted to the hospital because of a severe agitated depression of three-months' duration.

The diagnosis was involutional psychosis, melancholia.

July 25, 1949: 11:15 a. m.: A 100-mg. dose was administered.

11:45 a. m.: There was severe sweating but no other noticeable changes. Perspiration persisted until the time of retiring, at 9 p. m.

CASE 6.—A woman aged 69 was admitted to the hospital because of a very intense agitated depressed state of three-months' duration. In addition to her ceaseless activity, she was overtalkative, but the content was entirely self-deprecatory, hopeless, and suicidal. Sleep and appetite were poor.

The diagnosis was involutional psychosis, melancholia.

July 27, 1949: 11:00 a. m.: A 100-mg. dose was administered.

11:30 a. m.: Agitation diminished, and the patient was sleepy.

12:00 a. m.: The patient ate well, showed no agitation, and was much less depressed.

Afternoon: She showed no agitation, was cheerful, conversed well with other patients, ate well, and made no self-deprecatory remarks.

9:00 p. m.: She went to sleep promptly.

July 28: 10:50 a. m.: She received 150 mg. of the drug.

1:00 p. m.: Agitation was considerably diminished, but mild depression continued. The patient ate well.

1:15 a. m.: She awakened agitated and depressed again.

CASE 7.—A man aged 52 had an illness of one-month's duration. He had a history of a number of similar episodes, dating back 12 yr. In the hospital he was mildly depressed and agitated. There was self-blame, insomnia, and mild anorexia.

The diagnosis was manic-depressive psychosis, depressive type.

Aug. 13, 1949: 11:10 a. m.: He received 100 mg.

11:30 a. m.: He began to itch intensely all over, especially on the face and feet. He perspired profusely, complained of feeling dizzy and groggy and was ataxic.

12:00 noon: He was given tripelennamine ("pyribenzamine") hydrochloride, 50 mg. every four hours.

1:00 p. m.: His depression lifted. The patient felt cheerful and continued to feel well until the time of retiring. He slept well.

Aug. 14: His symptoms had returned.

CASE 8.—A man aged 35 had an illness of two-months' duration. He was moderately depressed, worried over finances, wished himself dead, and was anorexic, insomnic, and impotent. He had had one previous depression two years previously.

The diagnosis was manic-depressive psychosis, depressive type.

Nov. 6, 1949: 9 a. m.: A 50-mg. dose was administered.

10:00 a. m.: No change was noted except for complaints of shaking of the hands and paresthesias of the hands and feet.

2-9 p. m.: His spirits improved moderately. He slept well.

Nov. 7: 9:00 a. m.: He received 100 mg.

10:00 a. m.: The hands and feet felt as though "going to sleep."

11:00 a. m.-6:00 p. m.: Paresthesias gradually diminished. There was a slight improvement in mood.

CASE 9.—A woman aged 43 had an illness of one-year's duration. She was very depressed, retarded in both motor and psychic spheres, almost stuporous, fearful, and self-deprecatory and suffered from anorexia and insomnia.

The diagnosis was manic-depressive psychosis, depressive type.

May 12, 1949: 10:15 a. m.: She received 100 mg. of the drug. There was no significant change in behavior.

May 13: 7:15 a. m.: She received 100 mg.

9:00 a. m.: The patient was more alert, but the depression has not changed significantly.

May 14: 7:00 a. m.: She received 100 mg.

7:15 a. m.: A fine punctate rash appeared over the entire body with much itching. The rash and itch persisted all day. There was no significant change in behavior.

CASE 10.—A woman aged 24 had an illness of six-months' duration. She was depressed, self-blaming, fearful, and anorexic. She had a severe associational disturbance in thinking, a marked disturbance of attention, ideas of reference, delusions, hallucinations, and homicidal impulses.

The diagnosis was schizophrenia, paranoid type.

Oct. 31, 1949: 11:30 a. m.: A 100-mg. dose was administered.

11:50 a. m.: She had shaking and began to flush.

12:30-1:30 p. m.: Flushing of the face, tachycardia, dyspnea, and cyanosis occurred.

1:30 p. m.: The patient felt much better and appeared cheerful.

2:30 p. m.: The patient was cheerful, talkative, and friendly and entered into social activities (considerable improvement).

10:00 p. m.: She continued cheerful, talkative, and friendly.

Nov. 1: 8:40 a. m.: She received 50 mg.

9:30 a. m.-9:00 p. m.: Her mood was cheerful to euphoric. She was talkative and cooperative, friendly, and interested in social activities.

Nov. 2: 9:50 a. m.: She received 50 mg. of the drug.

10:30 a. m.: She was cheerful, friendly, and cooperative, this mood continuing throughout the day.

Nov. 3: 7:00-11:00 a. m.: She was cheerful, friendly, and cooperative.

11:00 a. m.: She was becoming quiet and withdrawn.

12:00 noon: She was depressed, did not converse, was withdrawn, and was unable to enter social activities. She spent most of her evening lying quietly on the bed.

Nov. 4: 8:45 a. m.: She received 50 mg. All her symptoms were present.

9:45 a. m.: She was friendly and cheerful.

11:45 a. m.: She complained of itching and tingling of the hands and feet; she continued to be cheerful.

1:45 p. m.: A sudden change in behavior occurred. She was unable to get up from the bed. Speech was incoherent. She was out of contact; the face was flushed, and tachycardia occurred. The reaction lasted about 20 min.

2:15 p. m.: She was again friendly, cheerful, and interested in ward activities, and conversed easily. This mood continued until bedtime, at 9 p. m.

Nov. 5: Forenoon: The patient continued to be cheerful and friendly.

2:00 p. m.: After her nap, she was depressed, withdrawn, and uncommunicative; all symptoms returned.

CENTRAL NERVOUS ACTION OF HYDANTOINS, OXAZOLIDINEDIONES AND THIAZOLIDONES

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DETROIT

THAT SEIZURE electroencephalographic patterns may be observed during sleep or by pentylenetetrazole (metrazol®) activation in epileptic patients with normal routine electroencephalograms [1] signifies the influence of nervous activity of other regions of the brain on epileptogenic foci in giving rise to clinical attacks.[2] It is not surprising, then, to see that an antiepileptic drug is efficacious in certain cases while effective in similar cases only with the addition of a sedative.[3] In rare instances, an agent which stimulates the central nervous system has also been found to be of value in combating epileptic convulsions.[4] In the discriminate management of epilepsy, therefore, a knowledge of the various actions of an anticonvulsant agent on the central nervous system is required.

In this paper, there will be presented results on the antimetrazol,® antielectroshock, and other actions on the central nervous system of the hydantoins, oxazolidinediones, and thiazolidones. It is hoped that the data will be of value to clinicians in the treatment of epilepsy.

EXPERIMENTAL STUDY

The antielectroshock activity of a compound was determined by its ability to raise the electroshock threshold in the cat by the method of Putnam and Merritt. In cases in which the amount of material was not sufficient for testing in the cat, the anticonvulsant activity was determined in mice by the method of Toman, Swinyard, and Goodman from the abolition of the extensor component of the convulsion.[5]

1. Gibbs, E. L., and Gibbs, F. A.: Diagnostic and Localizing Value of Electroencephalographic Studies in Sleep, A. Res. Nerv. & Ment. Dis., Proc. **26**:366, 1946. Merlis, J. K.; Henriksen, G. F., and Grossman, C.: Metrazol Activation of Seizure Discharges in Epileptics with Normal Routine Electroencephalograms, Electroencephalog. & Clin. Neurophysiol. **2**:17, 1950.

2. Walker, A. E., and others: Symposium: Thalamocortical Relationship, Introductory Remarks, Electroencephalog. & Clin. Neurophysiol. **1**:389, 1949.

3. Merritt, H. H.: Treatment of Epilepsy, Cincinnati J. Med. **27**:279, 1946.

4. Caveness, W.: A Therapeutic Approach Suggested by the Coincidence of Sleep and Convulsive Seizures, Tr. Am. Neurol. A. **74**:223, 1949.

5. (*a*) Putnam, T. J., and Merritt, H. H.: Experimental Determination of the Anticonvulsant Properties of Some Phenyl Derivatives, Science **85**:525, 1937. (*b*) Toman, J. E. P.; Swinyard, E. A., and Goodman, L. S.: Properties of Maximal Seizures, and Their Alterations by Anticonvulsant Drugs and Other Agents, J. Neurophysiol. **9**:231, 1946. (*c*) Chen, G., and Ensor, C. R.: Evaluation of Antiepileptic Drugs, Arch. Neurol. & Psychiat. **63**:56 (Jan.) 1950.

In screening compounds for anti-metrazol® activity, five fasted rats of the same sex, each weighing between 100 and 150 gm., were used for each dose level. The material in solution or in suspension with acacia was given by oral administration. Half an hour later, the metrazol® solution (93 mg. per kilogram in 10 cc. solution) was injected subcutaneously. This amount of metrazol® is a convulsant dose for 98 to 100% of the untreated rats. The animals were then observed for the time of onset and the severity of convulsions for 30 min. The convulsion was recorded as slight (jerking of the head, spasm of facial muscles, and raising of forelimbs), moderate (convulsions involving all the limbs), and frank (inability to stand and convulsive seizures).

Owing to the small number of animals employed, a rating system was used to indicate anti-metrazol® potency. It is based on the severity of convulsive seizures and the number of rats that are prevented from convulsions, as follows: 4+, complete protection of five rats; 3+, four rats protected; 2+, three rats protected; 1+, two rats protected, or one rat protected and marked suppression of convulsion in the other four animals.

For a quantitative comparison of anti-metrazol® activity, the 50% protective dose may be used. This was found for 3,5,5-trimethyl-2,4-oxazolidinedione (trimethadione) and phenobarbital to be 138.0 and 11.0 mg. per kilogram, respectively, as interpolated from the probit-log dose regression lines.[6]

RESULTS AND COMMENT

A. Hydantoins.—(*a*) 5,5-Substituted Hydantoins: The data for 5-substituted 5-phenyl- and 5,5-dialkyl-hydantoins are given in Tables 1 and 2, respectively. In accord with earlier observations, the phenyl group is essential both for anticonvulsant and for anesthetic action.[7] The hypnotic effect is greater for a compound with an alkyl chain containing less than three carbon atoms. Some of the compounds with long alkyl chains are central-nervous-system stimulants.[8] Whereas the anti-metrazol® activity is parallel with the general central-nervous-depressive action, it is not necessarily so in regard to antielectroshock potency. The 5,5-diphenylhydantoin, for instance, is very active against electroshock seizures; yet it produces convulsions in the cat at toxic dose levels.

It is of interest to note the recent reports on anti-metrazol® activities of the 5,5-substituted 2,4-dithiohydantoins.[9] In contrast with the corresponding diketohydantoins, the 5,5-dimethyl- and the 5,5-diethyl- dithiohydantoins are said to be more active than the 5,5-methylphenyl and the 5,5-ethylphenyl compounds.

(*b*) 3,5-Substituted 5-Phenylhydantoins: As the data in Table 3 show, the introduction of an alkyl or an aryl radical at the 3-position results in a slight decrease in anticonvulsant potency and a considerable reduction in hypnotic action. The methyl group is least influential. An exception is the case of 3-*n*-propyl-5-phenylhydantoin, which has an activity greater than that of the 5-phenyl compound.

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7. Novelli, N., and others: Chemical Constitution and Hypnotic Action, An. a. quim. Argentina **30**:225, 1942.

8. Merritt, H. H.; Putnam, T. J., and Bywater, W. G.: Synthetic Anticonvulsants, 5,5-Disubstituted Hydantoins Containing Hetero-Atom Inside Chain, J. Pharm. & Exper. Therap. **88**:67, 1945.

9. Hazard, R., and others: Action anticonvulsivante et structure moléculaire de quelques composés hélérocyclique pentagonaux, Compt. rend. Acad. sc. **228**:1762, 1949.

TABLE 1.—*Anticonvulsant Activity of 5-Substituted 5-Phenylhydantoins*

Substitution R	Antimetrazol* Mg./Kg.	Rating	Symptoms*	Antielectroshock (Cat)† Mg./Kg.	Rating	Symptoms
.....	500	2+	—	100	1+	—
Methyl	125	4+	—	80	—	Narcosis
	65	1+	—	40	3+	—
Ethyl	500	4+	Dp. dep.	50	4+	Md. dep.
	250	3+	Sl. dep.	25	2+	Sl. dep.
n-Butyl-thiomethyl	500	3+	Md. dep.	60	1+	—
	250	1+	—	...	...	..
Isoproxymethyl	250	—	—	100	4+	Dp. dep.
	...	...	..	50	2+	Sl. dep.
Thienyl	250	—	—	25	4+	—
	...	...	..	13	2+	—
Phenyl	250	—	—	25	4+	—
	...	...	..	13	3+	—
Diphenylene‡	500	—	—	100	2+	—
Phenethyl	500	—	Excitement	50	4+	Rigidity
	...	...	..	25	1+	—
Phenylthiomethyl	500	—	—	100	—	—

* Dp., Md., and Sl. dep. mean deeply, moderately, and slightly depressed.
† Cat, by the method of Putnam and Merritt.
‡ 5,5-Diphenylene hydantoin.

TABLE 2.—*Anticonvulsant Activity of 5,5-Dialkyl-Substituted Hydantoins*

Substitutions	Antimetrazol* Mg./Kg.	Rating	Symptoms	Antielectroshock (Cat) Mg./Kg.	Rating	Symptoms
5,5-Dimethyl	500	1+	—	100	—	—
5-Ethyl-5-(1-methoxypropyl)	500	—	—	100	1+	—
5-Butyl-5-(1-methoxypropyl)	500	—	—	100	1+	—
5-Sec. butyl-5-(1-methoxypropyl) ..	500	—	Excitement	100	—	—
5-Amyl-5-(sec. butoxymethyl)	500	—	Convulsion	100	—	Excitement
5-Isoamyl-5-(1-methoxypropyl) ...	500	1+	Sl. dep.	100	1+	Sl. dep.
1,5,5-Trimethyl	500	—	—	100	—	—
1,3,5,5-Tetramethyl	500	—	—	100	— - 1+	—

TABLE 3.—*Anticonvulsant Activity of 3,5-Substituted 5-Phenylhydantoins*

Substitutions R3	Substitutions R5	Antimetrazol* Mg./Kg.	Rating	Symptoms	Antielectroshock (Cat) Mg./Kg.	Rating	Symptoms
.....	.....	500	2+	—	100	1+	—
Methyl	.....	500	—	—	200	—	—
n-Propyl	.....	125	4+	—	100	1+	Sl. dep.
		65	3+	—	...	...	..
Allyl	.....	500	1+	—	200	1+	—
α-Naphthyl	.....	250	—	—	100	—	—
β-Naphthyl	.....	250	—	—	100	—	—
Phenyl	.....	250	—	—	200	1+	—
Methyl	Methyl	500	4+	Sl. dep.	50	4+	Ataxia
		250	4+	—	25	1+	—
		125	3+	—	...	...	..
Methyl	Ethyl	250	4+	Sl. dep.	50	4+	Sl. dep.
		125	2+	—	25	3+	—

(*c*) 1,5-Substituted 5-Phenylhydantoins: The 1-alkyl-5-phenylhydantoins are characterized by a strong hypnotic action. Hypnotic potency attains a maximum with three carbon atoms in the alkyl group; it then decreases with increasing

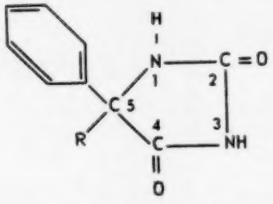

Fig. 1.—Formula for 5-substituted 5-phenylhydantoins.

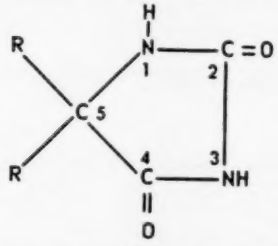

Fig. 2.—Formula for 5,5-dialkyl-substituted hydantoins.

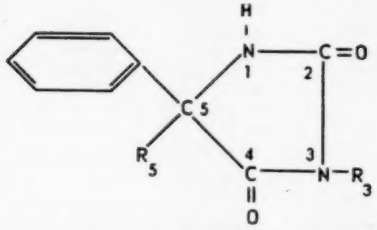

Fig. 3.—Formula for 3,5-substituted 5-phenylhydantoins.

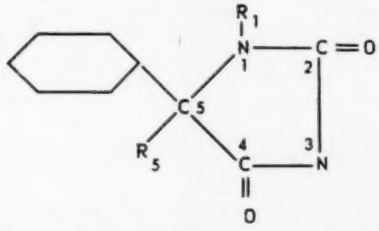

Fig. 4.—Formula for 1,5-substituted 5-phenylhydantoins.

length of the carbon chain (Table 4). The hypnotic and anesthetic activities of 1-*n*-propyl-5-phenyl-, 1-isopropyl-5-phenyl-, and 1-allyl-5-phenyl- hydantoins in mice, rats, rabbits, and dogs are given in Table 5. Surgical anesthesia promptly

follows the intravenous injection of 75 mg. per kilogram (dissolved in sodium hydroxide) of the three compounds. No disturbance in respiration or blood pressure is evident.

The anticonvulsant potencies of the 1-alkyl-5-phenylhydantoins are weak below hypnotic dose levels. The addition of another alkyl group at the 5-position gives rise to a decrease of both hypnotic and anticonvulsant activities. Another phenyl group at the 5-position abolishes the central-nervous-depressive action completely.

The results obtained with 1-substituted 5-α-thienylhydantoins (Table 6) are similar to those of their 5-phenyl analogues. The compounds with an alkyl chain

TABLE 4.—*Anticonvulsant Activity of 1,5-Substituted 5-Phenylhydantoins*

Substitutions		Antimetrazol®			Antielectroshock (Mouse)	
					PD_{50}	
R_1	R_5	Mg./Kg.	Rating	Symptoms	(Mg./Kg.)	Symptoms
.....	.....	500	2+	—	...	.....
Methyl	.....	65	4+	Sl. dep.	200	Sl. dep.
		33	1+	—	...	.....
Methyl	Methyl	65	4+	—	100	.....
		33	1+	—	...	.....
Methyl	Ethyl	250	3+	—	100	Sl. dep.
		125	1+	—	...	.....
Methyl	Propyl	250	—	—	200	Sl. dep.
Ethyl	.....	65	4+	—	75	Sl. dep.
		33	3+	—	...	.....
Ethyl	Methyl	250	3+	—	100	Sl. dep.
Ethyl	Ethyl	250	1+	—	150	Md. dep.
Ethyl	Propyl	250	1+	—	>350	—
Ethyl	Phenyl	250	—	—	200	—
Propyl	.....	65	4+	Md. dep.	200	Dp. dep.
		33	2+	—	...	.....
Propyl	Methyl	125	4+	—	150	Md. dep.
		65	2+	—	...	.....
Propyl	Ethyl	500	1+	—	>250	Sl. dep.
Propyl	Propyl	500	1+	—	>250	Sl. dep.
Allyl	.....	65	4+	Md. dep.	85	Sl. dep.
		33	2+	Sl. dep.	...	.....
Allyl	Methyl	65	4+	Sl. dep.	100	Md. dep.
		33	2+	—	...	.....
Allyl	Ethyl	125	4+	Sl. dep.	150	Sl. dep.
		65	2+	—	...	.....
Allyl	Propyl	250	1+	—	200	—
Isopropyl-	.....	125	4+	Sl. dep.	200	Dp. dep.
n-butyl	.....	250	2+	Sl. dep.	150	Sl. dep.
n-butyl	Methyl	250	1+	—	300	Sl. dep.
n-butyl	Ethyl	500	1+	—	400	—
n-butyl	Propyl	500	1+	—	Ineffective at 400	—
n-heptyl	.....	500	1+	—	Ineffective at 400	—
n-heptyl	Methyl	500	1+	—	400	Sl. dep.
n-heptyl	Ethyl	500	1+	Sl. dep.	100	Sl. dep.

of less than four carbon atoms are less depressive, while 1-*n*-butyl- and 1-β-phenethyl-5-α-thienyl- hydantoins are more depressive in their central-nervous action than the corresponding 1-substituted 5-phenylhydantoins.

B. 2,4-Oxazolidinediones.—Unlike the corresponding hydantoins, some of the 5,5-dialkyl-2,4-oxazolidinediones are potent hypnotic agents.[10] The 5,5-diphenyl compound is, however, weak in protecting against electroshock convulsions.[5c] One striking feature in the relation of chemical constitution to anticonvulsant activity of the 2,4-oxazolidinediones, as shown by the data in Table 7, is the enhanced

10. Stoughton, R. W., and Baxter, H. H.: The Hypnotic Action of Substituted Oxazolediones, J. Pharm. & Exper. Therap. **69**:304, 1940.

anti-metrazol* activity by the methyl group at the 3-position in 5-phenyl, 5,5-dimethyl, 5,5-methylethyl, 5,5-methylphenyl, and 5,5-ethylphenyl compounds. The 3,5-dimethyl-5-phenyl derivative is the most active anti-metrazol* agent in this group of substances. On the other hand, the 3-ethyl-5,5-dimethyl-, the 3-methyl-5,5-diphenyl-, and the 3-butyl-5,5-dipropyl- oxazolidinediones are less active both in anticonvulsant and hypnotic activities than the corresponding 5,5-substituted compounds.

TABLE 5.—*Central-Nervous-Depressing Effect* of 1-Propyl-5-Phenyl-, 1-Isopropyl-5-Phenyl-, and 1-Allyl-5-Phenyl-Hydantoins*

		1-Propyl-5-Phenyl			1-Isopropyl-5-Phenyl			1-Allyl-5-Phenyl		
Dose Mg./Kg.	Route	Depression	Recovery Av. Hr.	Mortality	Depression	Recovery Av. Hr.	Mortality	Depression	Recovery Av. Hr.	Mortality
A. Mice (10 Animals per Dose)										
54	Oral	0-2+	½	0/10	2+	½	0/10	2-3+	¾	0/10
70	Oral	1-2+	½	0/10	3+	1	0/10	3+	1	0/10
90	Oral	2-3+	2	0/10	3+	2½	0/10	3-4+	2	0/10
118	Oral	3+	3	0/10	4+	2½	0/10	4+	5½	0/10
154	Oral	4+	5	2/10	4+	5	0/10	4+	6	0/10
200	Oral	4+	8	0/10	4+	8+	1/10	4+	8+	0/10
		LD50 = 630 Mg./Kg. (Oral)			LD50 = 660 Mg./Kg. (Oral)			LD50 = 270 Mg./Kg. (Oral)		
54	I. P.†	1-2+	¾	0/10	3+	¾	0/10	3-4+	1	0/10
70	I. P.	3+	¾	0/10	3-4+	1¼	0/10	4+	1½	0/10
90	I. P.	4+	¾	0/10	4+	1¾	0/10	4+	3	0/10
118	I. P.	4+	2½	0/10	4+	3	0/10	4+	5	0/10
154	I. P.	4+	3½	0/10	4+	5	0/10	4+	8+	2/10
200	I. P.	4+	5½	0/10	4+	8+	1/10	4+	8+	3/10
B. Rats (5 Animals per Dose)										
40	I. P.	3-4+	½	0/5	...	...	....	3-4+	1-1½	0/5
54	I. P.	4+	1½	0/5	3-4+	1	0/10	4+	1-1½	1/5
70	I. P.	4+	1¾	0/5	4+	2½	0/10	4+	3	0/5
90	I. P.	4+	2	0/5	4+	2½	0/10	4+	3½	4/5
118	I. P.	4+	3½	3/5	4+	3½	1/10	4+	...	5/5
154	I. P.	4+	4½	4/5	4+	4	4/10	4+	...	5/5
200	I. P.	4+	5½	4/5	4+	6	4/10	4+	...	5/5
C. Rabbits (2 Animals per Dose)										
25	I. P.	...	...	...	1+	1	0/10	4+	1¼	0/2
50	I. P.	3+	1¼	0/2	1-2+	1¼	0/10	4+	2	0/2
100	I. P.	4+	3	0/2	3-4+	3	0/10	4+	2¾	1/2
200	I. P.	4+	6+	0/2	4+	6+	1/10	4+	...	2/2
25	I. V.‡	3+	¾	0/2	3+	¾	0/10	3+	1	0/2
50	I. V.	3+	1¼	0/2	3+	2½	0/10	3+	2½	0/2
100	I. V.	3+	2½	0/2	4+	3+	1/10	4+	...	2/2
D. Dogs (2 Animals per Dose)										
25	I. P.	2+	1	0/2	1+	1½	0/2	1+	¾	0/2
50	I. P.	4+	5	0/2	3+	1½-6	0/2	3+	1-4	0/2
100	I. P.	4+	...	2/2	4+	6	0/2	4+	...	2/2
200	I. P.	4+	...	2/2	4+	22	1/2	4+	...	2/2

* 1+ indicates slight ataxia; 2+, marked ataxia with some reflexes lost; 3+, hypnotic stage, and 4+, stage of anesthesia.
† I. P. means "intraperitoneal."
‡ I. V. means "intravenously."

As a class, the 2,4-oxazolidinediones are high in anti-metrazol,* but low in antielectroshock, activity.

The 3,5,5-trimethyl- 2,4-thiazolidinedione is reported as being unable to antagonize the convulsive action of metrazol*.[9] Here the methyl group at the 3-position reduces the anticonvulsant action of the 5,5-dimethyl compound.

C. 4-Thiazolidone.—Some of the 4-thiazolidone derivatives with a phenyl group at the 2-position and an alkyl group at the 3-position are fairly active anti-metrazol* agents. The 2-phenyl-3-ethyl-4-thiazolidone and its sulfone are equal to 3,5,5-trimethyl-2,4-oxazolidinedione in anti-metrazol* activity and are more effective

than the latter in suppressing electroshock convulsions. The lengthening of the alkyl chain or oxidation of the sulfur atom reduces the central-nervous-depressive action.

From the central-nervous-depressive properties of the three classes, as here given, and from the clinical results for some of these compounds in the treatment

TABLE 6.—*Anticonvulsant Activity of 1-Substituted 5-α-Thienylhydantoins*

Substitutions	Antimetrazol®			Antielectroshock (Cat)		
R_1	Mg./Kg.	Rating	Symptoms	Mg./Kg.	Rating	M. T. D.
.....	500	3+	Sl. dep.	100	—	—
	250	2+	—	...	...	..
Methyl	250	4+	Sl. dep.	200	2+	200
	125	2+	—	100	1+	..
Ethyl	125	4+	Sl. dep.	100	4+	50
	65	3+	—	50	1+	..
n-Propyl	125	3+	Sl. dep.	100	4+	50
	63	1+	—	50	1+	..
Isopropyl	250	4+	Md. dep.	100	2+	50
	125	3+	Sl. dep.	50	1+	..
Allyl	125	4+	Sl. dep.	100	3+	50
	63	3+	—	50	2+	..
n-Butyl	250	4+	Dp. dep.	100	1+	50
	125	1+	Sl. dep.	50	1+	..
β-Phenethyl	250	3+	Sl. dep.	200	1+	200
	125	1+	—	...	...	..
Benzyl	500	4+	Dp. dep.	200	1+	200
	250	2+	Sl. dep.	...	...	..

TABLE 7.—*Anticonvulsant Activity of 3,5-Substituted 2,4-Oxazolidinediones*

Substitutions			Antimetrazol®			Antielectroshock (Mouse)	
R_3	R_5	R_5	Mg./Kg.	Rating	Symptoms	PD_{50} (Mouse)	Symptoms
Methyl	Methyl	Methyl	250	4+	—	980	Sl. dep.
			125	2+	—	...	..
Methyl	Methyl	Ethyl	125	4+	—	400	Sl. ataxia
			65	1+	—	...	..
Ethyl	Methyl	Methyl	500	—	—	...	..
Butyl	Propyl	Propyl	500	2+	—	>400	—
.....	Phenyl	.....	500	1+	—	400	—
Methyl	Phenyl	.....	500	4+	—	400	—
			250	3+	—	...	..
Allyl	Phenyl	.....	500	3+	—	300	Sl. ataxia
.....	Methyl	Phenyl	250	4+	—	400	Sl. dep.
			125	3+	—	...	..
			65	2+	—	...	..
.....	Ethyl	Phenyl	250	4+	Lethal	200	—
			125	1+	—	...	..
Methyl	Methyl	Phenyl	125	4+	Sl. dep.	200	—
			65	4+	—	...	..
			33	2+	—	...	..
Methyl	Ethyl	Phenyl	250	4+	—	350	—
			125	2+	—	...	..
.....	Phenyl	Phenyl	500	1+	—	700	Sl. dep.
Methyl	Phenyl	Phenyl	500	—	—	...	..

of epileptic conditions, it appears unequivocal that the electroshock procedure is a fairly accurate laboratory method for the appraisal of substances for control of grand mal epilepsy. There seems to be no notable advantage in the technical nature of the electroshock procedure. The requirement is a high antielectroshock activity devoid of hypnotic action. A slight sedative effect, however, is beneficial in some patients.

The specificity of the anti-metrazol® test for evaluating anti-petit-mal agents may be questioned. Carbromal (bromdiethylacetylurea) in nonhypnotic doses, for instance, has been shown to be more effective than 3,5,5-trimethyl-2,4-oxazolidinedione against metrazol® convulsions.[5c] Yet carbromal is ineffective in alleviating petit mal attacks.[11] Thus, a substance which is specific against metrazol® may be useless to control petit mal seizures. The fact that a number of the anti-metrazol® substances are also effective anti-petit-mal agents requires further elu-

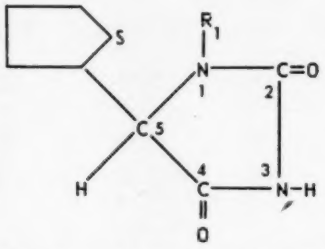

Fig. 5.—Formula for 1-substituted 5-α-thienylhydantoins.

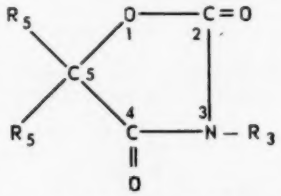

Fig. 6.—Formula for 3,5-substituted 2,4-oxazolidinediones.

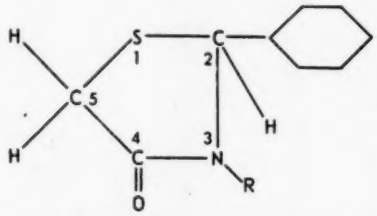

Fig. 7.—Formula for 2-phenyl-3-substituted 4-thiazolidone and 2-phenyl-3-substituted 4-thiazolidonesulfones.

cidation. It is possible that the epileptic foci giving rise to petit mal attacks are situated at a region where metrazol® exerts its action. Apparently, the active anti-petit-mal drugs so far available depress the increased irritability of all these centers.

In summarizing the central-nervous-depressive action of the hydantoins, 2,4-oxazolidinediones, and 4-thiazolidone, the following statements may be made:

11. Sharp, E. A.: Personal communication to the authors.

1. The 5-alkyl- or aryl- and 5-phenyl- hydantoins are active agents against electroshock convulsions. An additional phenyl or thienyl radical at the 5-position is more effective than a methyl or an ethyl group in enhancing antielectroshock activity. The introduction of a methyl group at the 3-position results either in no change in anticonvulsant activity with a reduction in hypnotic action or in a decrease of both. The 1-alkyl-5-phenyl compounds are potent hypnotics. A maximal hypnotic and anesthetic activity is attained with a propyl or an allyl chain at the 1-position.

TABLE 8.—*Anticonvulsant Activity of 2-Phenyl-3-Substituted 4-Thiazolidone and 2-Phenyl-3-Substituted 4-Thiazolidonesulfones*

3-Substitution (4-Thiazolidone)	Antimetrazol®			Antielectroshock (Cat)		
	Mg./Kg.	Rating	Symptoms	Mg./Kg.	Rating	M. T. D.*
Methyl	250	4+	Dp. dep.	100	4+	>100
	125	3+	—	50	1+	.....
Ethyl	250	4+	Sl. dep.	100	4+	<100
	125	2+	—	50	1+	.....
Propyl	250	4+	—	100	1+	<100
	125	1+	—	...	...	.....
Butyl	250	2+	—	100	1+	<100
	125	—	—	...	...	.....
Benzyl	500	—	—	100	—	>100
(4-Thiazolidonesulfone)						
Methyl	500	—	Sl. dep.	100	1+	>100
	250	—	—	...	...	.....
Ethyl	250	4+	—	100	1+	>100
	125	2+	—	...	...	.....
Propyl	250	4+	—	100	1+	>100
	125	1+	—	...	...	.....
Butyl	500	—	—	100	1+	<100
Benzyl	500	—	—	100	—	>100

* Minimal electroshock threshold dose.

2. The 2,4-oxazolidinediones are active anti-metrazol,® but weak antielectroshock, agents. In contrast with the hydantoins, the presence of a methyl group at the 3-position increases greatly the anti-metrazol® activity of some of the 5,5-substituted 2,4-oxazolidinediones. In these compounds the phenyl group at the 5-position lends only a slight increase in effectiveness in prevention of electroshock convulsions.

3. The 2-phenyl-3-ethyl-4-thiazolidone and its sulfone are as effective as the active, 2,4-oxazolidinediones against metrazol® and are more effective against electroshock convulsions.

Dr. H. R. Henze furnished the supply of 5-alkyl-5-alkoxyhydantoins; Dr. M. A. Spielman the supply of 3,5,5-trimethyl- and 3,5-dimethyl-5-ethyl-2,4-oxazolidinediones; Dr. Melvin Thorpe, the supply of 3,5,5-alkylaryl-2,4-oxazolidinediones, and Dr. L. M. Long and his associates, the other compounds used in the investigation.

OPHTHALMOPLEGIA INTERNUCLEARIS ANTERIOR WITHOUT A LESION OF THE POSTERIOR LONGITUDINAL BUNDLE

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NEW YORK

ONLY A FEW cases (20) of ophthalmoplegia internuclearis anterior have been reported. In most of these cases lesions have been present in the brain stem. In only five cases could no pertinent lesions of the brain stem be demonstrated. Another such case should be of interest. Lhermitte [1] introduced the term "internuclear ophthalmoplegia," and Lutz [2] divided the internuclear ophthalmoplegias into two types, posterior and anterior. The former refers to inability of the eye to abduct on conjugate lateral gaze without the presence of diplopia; the latter, to inability of the eye to adduct on conjugate lateral gaze without the presence of diplopia and with retention of the function of the internal rectus muscle in convergence. The condition may be unilateral or bilateral.

Various investigators have noted paralysis of lateral conjugate gaze with the preservation of convergence. A tumor of the pons was found in Quioc's [3] case of paralysis of conjugate gaze to the left. The nucleus of the abducens nerve was intact. Jolly's [4] patient, with paralysis of lateral gaze to the left, had a glioma of the pons with destruction of the nucleus of the abducens nerve on the left side; the nucleus of the abducens nerve on the right side was partly involved. The ocular findings in Wernicke's [5] patient were paralysis of all ocular movements with intact convergence. A tumor was present in the midline of the pons below the fourth ventricle. In Ewald's [6] case of paralysis of associated eye movements to the left with normal convergence, a pea-sized tubercle was shown in the pons. In Bruce's [7] patient the ocular findings were complete paralysis of conjugate move-

From the Neuropsychiatric Service of the Morrisania City Hospital; N. Savitsky, M.D., Director.

1. Lhermitte, J. J.: L'encéphalité léthargique: Questions neurologiques d'actualité, in Vingt conférences faites à la Faculté de Médécine de Paris (1921), Paris, Masson & Cie, 1922.

2. Lutz, A.: Über die Bahnen der Blickwendung und deren Dissoziierung. (Nebst Mitteilung eines Falles von Ophthalmoplegia internuclearis anterior in Verbindung mit Dissoziierung der Bogengänge), Klin. Monatsbl. Augenh. **70**:213, 1923.

3. Quioc: Mémoire sur la déviation conjuguee des yeux et la rotation de la face dans les lésions bulbo-protubérantielles, à propos d'une tumeur de cette région, Lyon méd. **37**:385, 1881.

4. Jolly, F.: Über einen Fall von Gliom im dorsalen Abschnitt des Pons und der Medulla oblongata, Arch. Psychiat. **26**:619, 1894.

5. Wernicke, O.: Über Lähmung der Seitwärtswender, Arch. Augenh. **42**:183, 1900.

6. Ewald: Demonstration eines isolierter kirschkerngrossen Tuberkel im Pons bei associierter Seitwärtslähmung des linken Auges, Verhandl. Berl. med. Gesellsch. **32**:176, 1901.

7. Bruce, A.: A Case of Double Paralysis of the Lateral Conjugate Deviation of the Eyes, Rev. neurol. & psychiat. **1**:329, 1903.

ments of the eyes to the left and slight paralysis of conjugate movements to the right. Convergence was preserved. Autopsy revealed tuberculous meningitis. A tubercle was seen in the pons projecting into the fourth ventricle. It occupied the position of the nuclei of both the sixth and the seventh cranial nerves, as well as the posterior longitudinal fasciculus (fasciculus longitudinalis medialis) on both sides. There was ascending and descending degeneration of both posterior longitudinal bundles. The third nerve was normal. Raymond and Cestan's [8] patient had paralysis of associated eye movements, especially to the right, with preservation of convergence. A tubercle was demonstrated in the tegmentum of the inner aspect of the pons. The third and sixth cranial nerves and their nuclei were unaffected. The authors stated that the paralysis of the associated eye movements was due to internuclear lesions without implication of the ocular nerves. Seggel's [9] patient showed paralysis of the right abducens nerve and of associated movements to the right. Convergence was good. Necropsy disclosed a tubercle on the right side of the pons, extending over as far as the left-facial-nerve fibers. It crossed the midline and destroyed the nucleus of the left sixth cranial nerve. In addition to other symptoms, the patient of Potts and Spiller [10] had paralysis of associated eye movements to the left with relatively good convergence. Necropsy revealed a tubercle in the tegmentum of the pons, which involved the left posterior longitudinal bundle in its upper part. The sixth cranial nerve showed degeneration. Grasset and Gaussel's [11] patient had bilateral paralysis of associated lateral eye movements with normal convergence. Multiple tubercles were demonstrated in the left cerebellar hemisphere, in the pons, and at the base of the fourth ventricle, with destruction of the nucleus of the abducens nerve bilaterally. Bertelsen and Rönne's [12] patient, with alcoholic polioencephalitis, had bilateral associated paralysis of volitional and reflex conjugate gaze. Convergence was preserved. Histologic sections showed encephalitic changes in the region of the hypoglossal nucleus, with slight involvement in the region of the nucleus of the sixth nerve. The authors attributed the degeneration of both posterior longitudinal bundles to a toxin. A tubercle was present in the right eminentia teres (eminentia medialis) in Noceti's [13] case of paralysis of gaze to the left with intact convergence. Wilbrand and Saenger's [14] patient, with paralysis of conjugate gaze to the left with intact convergence, showed a tumor, the size of a nut, in the pons. In Bollack's [15] case of paralysis of conjugate lateral gaze

8. Raymond, and Cestan, M. R.: Sur un nouveau cas de paralysie des mouvements de latéralité des globes oculaires, Rev. neurol. **11**:644, 1903.

9. Seggel: Doppelseitige Abduzens-und seitliche Blicklähmung, München. med. Wchnschr. **50**:772, 1903.

10. Potts, C. S., and Spiller, W. G.: A Case of Solitary Tubercle of the Pons: Remarks on the Pathway for Sensations of Taste from the Anterior Portion of the Tongue, Univ. Pennsylvania M. Bull. **16**:362, 1903.

11. Grasset, J., and Gaussel, A.: Paralysie des deux hémioculomoteurs (abolition des mouvements de latéralité à droite et à gauche): Tubercule de la protubérance, Rev. neurol. **13**:69, 1905.

12. Bertelsen, E., and Rönne, H.: Ein Fall Polioencephalitis mit assoziierter Blicklähmung supranuklearen Ursprungs, Monatsschr. Psychiat. u. Neurol. **25**:148, 1909.

13. Noceti, A.: Contribucion al estudio de los tumores del puente, Arch. oftal. hispano-america **12**:3, 1912.

14. Wilbrand, H., and Saenger, A.: Die Neurologie des Auges, München, J. F. Bergmann, 1921, Vol. 8, p. 62.

15. Bollack, J.: Syndrome de la partie inférieure de la calotte protubérnatielle avec paralysie des mouvements de latéralité des yeux, Rev. neurol. **31**:326, 1924.

with preservation of convergence, a glioma of the pons implicating the posterior longitudinal bundle was demonstrated. Freeman,[16] in an excellent paper on paralysis of conjugate gaze, added a case in Spiller's service, of a patient who two months prior to death had complete paralysis of conjugate gaze to the left with preservation of convergence, in addition to other signs, which had been present for over five years. A glioma of the pons was demonstrated. The posterior longitudinal bundle, as seen with the naked eye, was smaller and paler on the left than on the right. The left bundle was reduced in size, vacuolated, and replaced to a large extent by glia. The right posterior longitudinal bundle, while not entirely normal, showed much less advanced change. Van Gehuchten [17] described a patient who had, in addition to numerous other neurological signs, paralysis of conjugate gaze and good convergence. A tuberculoma was observed in the brain stem, which involved the posterior longitudinal bundle. Froment, Dechaume, and Colrat [18] reported two cases of paralysis of conjugate lateral gaze with intact convergence. A glioma of the pons was present in one and a tuberculoma of the pons in the other. Reese and Yaskin [19] described a case of paralysis of all lateral movements of the eyes with normal convergence, due to an intramedullary pontine tumor. They postulated involvement of the posterior longitudinal bundles caudal to the levels of the third-cranial-nerve nuclei, and possibly of both centers for lateral deviation of the eyes. Freeman, Ammerman, and Stanley [20] reported three cases of paralysis of associated lateral movements of the eyes with preservation of convergence. The lesions were stated to be in the tegmentum of the pons, interrupting to a greater or less extent the medial longitudinal bundle. In one case autopsy showed destruction of the bundle on the right side by hemorrhage.

In Spiller's [21] case of bilateral ophthalmoplegia internuclearis anterior the tegmentum was softened at the level of the corpora quadrigemina. The nucleus of the left trochlear nerve was destroyed in its lower part and extensively degenerated in its upper part. The area of softening at the level of the trochlear nucleus destroyed most of the left posterior longitudinal bundle and invaded the right one as well. Spiller attributed the ocular difficulties to the involvement of the posterior longitudinal bundle. In Cogan, Kubik, and Smith's [22] first case, that of a patient with lupus erythematosus, a small infarct was observed involving the fasciculus longitudinalis medialis on the side of the unilateral internuclear ophthalmoplegia.

16. Freeman, W.: Paralysis of Associated Lateral Movements of the Eyes, Arch. Neurol. & Psychiat. **7**:454 (April) 1922.

17. van Gehuchten, P.: Un cas de paralysie latérale du regard lésion protubérantielle; contribution à l'étude des voies oculogyres, Rev. d'oto-neuro-opht. **8**:701, 1930.

18. Froment, J.: Dechaume, J., and Colrat, A.: Deux observations anatomo-cliniques de paralysie des mouvements associés de latéralité des yeux, Rev. d'oto-neuro-opht. **8**:713, 1930.

19. Reese, W. S., and Yaskin, J. C.: Preservation of Convergence with Paralysis of all Lateral Movements in a Case of Intramedullary Tumor of the Pons, Am. J. Ophth. **24**:544, 1941.

20. Freeman, W.; Ammerman, H. H., and Stanley, M.: Syndromes of the Pontile Tegmentum: Foville's Syndrome: Report of Three Cases, Arch. Neurol. & Psychiat. **50**:462 (Oct.) 1943.

21. Spiller, W. G.: Ophthalmoplegia Internuclearis Anterior: A Case with Necropsy, Brain **47**:345, 1924.

22. Cogan, D. C.; Kubik, C. S., and Smith, W. L.: Unilateral Internuclear Ophthalmoplegia, Arch. Ophth. **44**:783 (Dec.) 1950.

Bender and Weinstein [23] demonstrated paralysis of adduction with intact convergence and nystagmus in the abducting eye in experimentally destructive lesions of the medial aspect of the posterior longitudinal bundle in the monkey.

REPORT OF A CASE

A Negro aged 20 was admitted to the Morrisania City Hospital on May 28, 1947, with the complaint of stiffness of the neck of four-weeks' duration. The patient was in prison four weeks prior to admission for a minor offense. There he had chills, fever, nausea, and vomiting, with pain and stiffness of the neck. He also began to tilt his head to the left. A moist, productive cough appeared at the same time. He was transferred to the prison hospital, where he remained for two weeks, and from which he was discharged on May 27, with the diagnosis of hysterical torticollis.

The previous history included the occurrence of a blow to the head by his father at the age of 9 yr. There were no immediate or delayed complaint from this trauma.

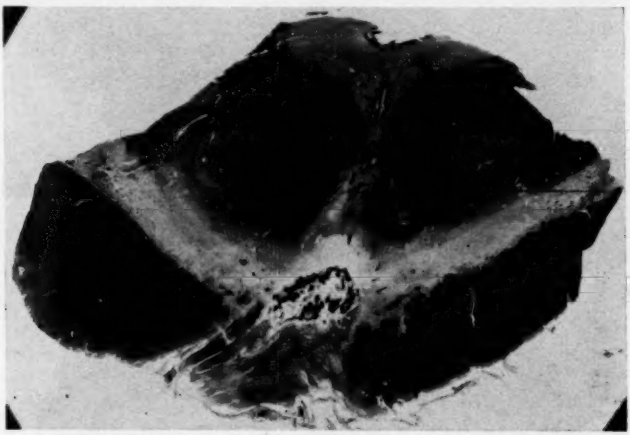

Fig. 1.—Midbrain.

The family history was noncontributory.

On admission the patient appeared chronically ill. The temperature was 102 F.; the pulse rate, 104; the blood pressure, 100/70 (Hg), and the respiration rate, 28. The right side of the chest was less developed and smaller than the left. Coarse rhonchi were heard bilaterally on auscultation.

Neurologic examination showed the patient to be conscious and cooperative. He answered questions on request and was oriented. At times he was somewhat listless. His head and neck were rotated to the left. There was slight stiffness of the neck, and Kernig's sign was elicited bilaterally. The right pupil was slightly larger than the left; both reacted to light. He was unable to adduct either eye when being tested for conjugate lateral movements. Convergence was intact. No diplopia was found with the red-glass test. No constriction of the visual fields on the confrontation test was demonstrated. Bilateral papilledema, with hemorrhages in the right fundus, was noted. Both corneal reflexes were depressed. The palate moved well, and the tongue was in the midline. There was no facial weakness. No pathologic (plantar) responses were elicited. There was no ataxia in the finger-to-nose or the heel-to-knee test. Sensation was

23. Bender, M. B., and Weinstein, E.: Effects of Stimulation and Lesion of the Median Longitudinal Fasciculus in the Monkey, Arch. Neurol. & Psychiat. **52**:106 (Aug.) 1944.

normal. The diagnosis of a probable tumor of the posterior fossa, possibly a tuberculoma, was made. A spinal puncture was done to exclude tuberculous meningitis. The spinal-fluid pressure was greater than 650 mm. of water but was not recorded; only a few drops were removed for a cell count. The fluid was clear, and no cells were found. Urinalysis and blood chemistry deter-

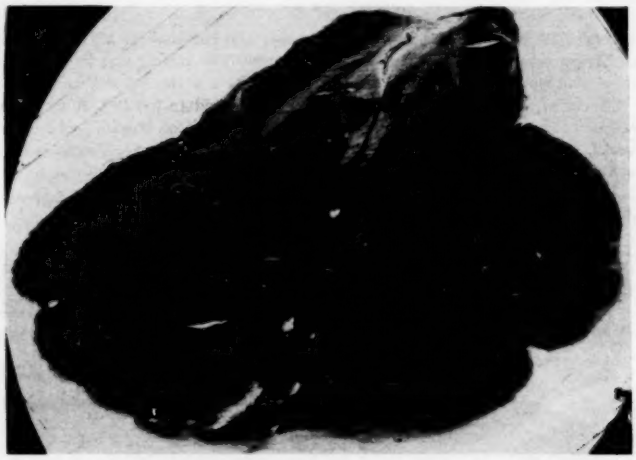

Fig. 2.—Upper part of pons. The distortion is due to fixation.

Fig. 3.—Medulla oblongata at level of the olivary nuclei.

minations did not disclose any significant changes. The serologic reactions of the blood were negative.

On May 30, ventriculography was performed through a trephine opening in the left posterior-parietal area. The roentgenograms showed dilatation of the entire extent of both lateral ventricles and the third ventricle. The findings suggested a block below the third ventricle. A suboccipital

craniectomy was done on the same day. The cerebellar tonsils were found to be below the level of the foramen magnum. The convolutions of the left cerebellar hemisphere were larger than those on the right. The pia-arachnoid of the left cerebellar hemisphere was nicked, and a needle was inserted. At a distance of 2 cm. increased resistance was encountered. The cerebellum was incised, and a large firm mass was encountered and removed. The patient died at the conclusion of the operation.

Autopsy revealed three ovoid, firm nodular masses in the adrenal glands. The right lung showed considerable edema and congestion. The hilar and peribronchial nodes of the lower lobe of each lung were enlarged and replaced by nodular tumors, similar to those present in the adrenal glands. On incision of these tumors, caseation was noted in their interior, and histologic study showed typical tuberculosis.

On histologic study, the cerebellar tumor proved to be a tuberculoma. The sections of the right third frontal cortical convolution revealed a tuberculoma, with caseous necrosis in the center and granulation tissue, with many Langhans giant cells, in the periphery. The remainder of the cortex was normal. The cerebellar white matter contained numerous fresh ring hemorrhages. Perivascular collars of lymphocytes surrounded many vessels.

The midbrain, pons, and medullary segments of the brain stem were neither enlarged nor diminished in size. Transverse sections of these regions disclosed no hemorrhages, softenings, or nodules. Sections through the midbrain were normal with both cresyl violet and myelin-sheath stains, as were sections of the pons and medulla. The nuclei of the third, fourth, and sixth cranial nerves were within normal limits. There were no signs of involvement of the posterior longitudinal fasciculi by ascending or descending degeneration, at these levels.

Figures 1, 2, and 3, taken at the levels indicated, show intactness of the brain stem, including the posterior longitudinal bundles.

COMMENT

Clinical reports of transitory ophthalmoplegia internuclearis anterior, indicating a reversible lesion in the posterior longitudinal bundle or interference in its conduction system, have been recorded in cases of head injury (Bielschowsky [24]), disseminated (multiple) sclerosis (Jaensch,[25] Moncreiff,[26] Wilbrand and Saenger,[27] Antoni,[28] Gayle and Ourgaud [29]), and encephalitis (Lutz,[30] Jaensch,[25] Wilbrand and Saenger [31]). Lutz,[30a] in discussing his previous case (1923), stated that a toxin from the encephalitis affected the bundle. Lemere [32] described a patient who was unable to look upward or laterally; convergence was normal. He postulated a congenital weakness of the fibers of the posterior longitudinal bundle which did not result in signs except on two occasions, when the patient had an infection of

24. Bielschowsky, A.: Die Innervation der Musculi recti interni als Seitenwender, Sitzungsb. d. ophth. Gesellsch., p. 164, 1902.

25. Jaensch, P. A.: Zur Klinik der supranuclearen Medialisparese und internuclearen Ophthalmoplegie, von Graefes Arch. Ophth. **125**:592, 1930-1931.

26. Moncreiff, W. F.: Ophthalmoplegia Internuclearis and Other Supranuclear Paralyses of the Eye Movements, Arch. Neurol. & Psychiat. **25**:148 (Jan.) 1931.

27. Wilbrand and Saenger,[14] p. 70.

28. Antoni, N.: Eine eigenartige symmetrische Motilitätsstörung der Augen (Syndrom der internukleären Unterbrechung des hinteren Längsbündels), Jahrb. Psychiat. u. Neurol. **45**:15, 1927.

29. Gayle, G. E., and Ourgaud, A. G.: Essai de classification des troubles oculomoteurs du regard horizontal, à propos de deux nouveaux cas de syndrome de foville atypique, Rev. d'oto-neuro-opht. **21**:86, 1949.

30. Lutz, A.: (*a*) Über doppelseitige Ophthalmoplegia internuclearis. (Mitteilung einer weiteren Beobachtung), von Graefes Arch. Ophth. **118**: 470, 1927; (*b*) footnote 2.

31. Wilbrand and Saenger,[14] p. 65.

32. Lemere, F.: Ophthalmoplegia Internuclearis, Arch. Neurol. & Psychiat. **50**:585 (Nov.) 1943.

the upper respiratory tract. Then the syndrome of ophthalmoplegia internuclearis anterior appeared. Fatigue seemed to be the largest single factor. Since the present patient had had no difficulty with his eyes prior to his terminal illness, it is unlikely that the ocular signs had a congenital basis, as reported by Dupuy-Dutemps.[33]

It was somewhat surprising to find no lesions of the posterior longitudinal bundles or elsewhere in the brain stem in the present case. However, paralysis of conjugate gaze with no lesions in the brain stem has been reported. Panas'[34] patient was unable to move the eyes separately or conjugately in the horizontal plane; vertical movements were normal. Softening of the cortical layers of the left cerebellar hemisphere and part of the inferior portion of the vermis was described. The cerebrum and brain stem were normal. The cases of Prevost[35] and Urbantschitsch[36] are suggestive, but no definite statement as to the brain stem is indicated. In the former case, the patient had paresis of the right limbs, and conjugate deviation of the eyes to the left, with inability to move them to the right. A tumor was found in the right cerebellar hemisphere. In the latter, the patient was unable to move the eyes to the left. An abscess was demonstrated in the left cerebellar hemisphere. Savitsky and Rangell[37] found no lesions of the posterior longitudinal bundle in a patient with multiple sclerosis who had monocular nystagmus and paralysis of the right internal rectus of supranuclear type. Although such factors as possible congenital weakness of the bundle or a toxic action on it, as postulated by Lutz,[30a] cannot be excluded, I believe that functional impairment of the bundle may take place as a result of pressure on the brain stem by expanding lesions in the posterior fossa. Lewandowsky[38] indicated that paralysis of conjugate gaze may result from lesions at a distance, due to compression of the brain stem. Gaussel[39] stated that the paralysis of conjugate gaze in the case of Panas may have been due to compression of the brain stem. Bucy and Weaver[40] reported ipsilateral paralysis of conjugate lateral movements of the eyes in three patients with cerebellar abscesses, the paralysis disappearing after operation. It was these authors' belief that the paralysis arose as a result of compression of the pons with implication of the abducens nuclei and the posterior longitudinal bundles. Savitsky and Madonick[41] described divergence paralysis, a conjugate movement mediated

33. Dupuy-Dutemps, L.: Paralysie cóngenitale des mouvements de latéralité des yeux avec paralysie faciale unilatérale, Bull. Soc. opht. Paris, p. 365, 1934.

34. Panas, F. Perte des mouvements horizontaux des yeux; altération (ramollissement) du cervelet, Bull. et mém. Soc. chir. Paris **1**:433, 1875.

35. Prevost, J. L.: De la deviation conjuguée, des yeux et la rotation de la tête dans certains cas d'hémiplegie, Thèse de Paris, 1868.

36. Urbantschitsch, E.: Linkseitiger Kleinhirnabscess bei einem 8-jährigen Kinde mit kompressorischem Verschluss des Foramen Magendie, Parese des linken Abducens und rechten Internus, Monatsschr. Ohrenh. **49**:736, 1915.

37. Savitsky, N., and Rangell, L.: The Ocular Findings in Multiple Sclerosis, A. Res. Nerv. & Ment. Dis., Proc. **28**(1948):403, 1950.

38. Lewandowsky, M.: Handbuch der Neurologie, Berlin, Julius Springer, 1910, Vol. 1, Pt. 2, p. 734.

39. Gaussel, A.: Le paralysie des mouvements de latéralité des yeux, Rev. med. **25**:809, 1905.

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by the brain stem, through compression of the brain stem by neoplasms of the posterior fossa. Potts and Spiller [10] considered paralysis of lateral associated eye movements an intrapontine sign and advised against operation in patients showing this sign. Freeman [16] held a similar view; he stated:

> . . . Clear-cut paralysis of associated lateral movements with preservation of the power of convergence means a lesion of the posterior longitudinal bundle. This tract lies just to the side of the raphé of the pons, immediately under the floor of the fourth ventricle and the gray matter of the aqueduct of Sylvius. Hence it is one of the most inaccessible portions of the brain, quite beyond the reach of surgery.

The case reported shows that even the presence of ophthalmoplegia internuclearis anterior should not necessarily exclude operation, since the ocular phenomenon may result from compression of the brain stem by a tumor of the posterior fossa.

SUMMARY AND CONCLUSION

A case of bilateral ophthalmoplegia internuclearis anterior in a patient with a large tuberculoma of the cerebellum and, in addition, a smaller one in the right third frontal convolution and scattered tuberculomas of the viscera is described. Careful histologic study failed to reveal any lesion of the posterior longitudinal bundle (fasciculus longitudinalis medialis) or elsewhere in the brain stem.

It is reasonable to postulate that compression of the brain stem by a tumor of the posterior fossa may cause functional interference in the posterior longitudinal bundles without anatomic changes. Hence, the presence of ophthalmoplegia internuclearis anterior is not necessarily a contraindication to surgical intervention.

Dr. H. M. Zimmerman and Dr. M. Netsky, of the Department of Pathology of the Montefiore Hospital for Chronic Diseases, assisted in the neuropathologic examinations in this case.

HEREDITARY SPASTIC PARAPLEGIA AND HEREDITARY ATAXIA

A Family Demonstrating a Variety of Phenotypic Manifestations

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AND
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ST. LOUIS

SINCE Seeligmüller [1] described the clinical, and Strümpell [2] the pathological, characteristics of hereditary spastic paraplegia, an extensive literature on the subject has developed, and clinical reviews have appeared by Rhein,[3] Paskind and Stone,[4] and Jackson.[5] The genetic, as well as the clinical, aspects of the disorder have been analyzed by Bell and Carmichael.[6]

Strümpell [7] originally described two varieties of spastic paraplegia, one developing in adult life, the other in childhood and associated with mental retardation. Rhein [3] separated the cases in the literature into seven groups, distinguished by arbitrary anatomicoclinical criteria. Bell and Carmichael [6] divided these hereditary diseases into two major genetic classes, showing recessive and dominant characteristics, respectively. Each class was further subdivided into types, designated as Friedreich's ataxia (hereditary sclerosis, spinal form), spastic ataxia, and spastic paraplegia, the last designation being justified only by the absence of ataxia. These authors believed that the first two types, and probably the third, arise from the same gene under the influence of modifiers. However, they noted that, although Friedreich's ataxia and spastic ataxia are commonly found in the same stock, the latter and spastic paraplegia are not. Sjögren [8] believed that Friedreich's and Marie's

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disease (hereditary sclerosis, cerebellar form) are genetically distinct. Haldane [9] demonstrated partial sex-linkage in recessive spastic paraplegia and suggested that different main genes operate in different stocks in association with modifiers.

Roth [10] reported families in which Friedreich's disease, Charcot-Marie-Tooth atrophy (progressive neuropathic muscular atrophy), and Marie's ataxia were associated, and he discussed at length the data in the literature concerning various clinical manifestations in the same stock. He also made valuable observations concerning the relation of normal aging to the abiotrophies. André-van Leeuwen and van Bogaert [11] discussed the relation of optic nerve atrophy with hereditary ataxia to Leber's disease (hereditary optic atrophy), and of some striatal degenerations to cerebellar involvement.

Recently, Garland and Astley [12] reported a family with a dominantly inherited spastic paraplegia, amyotrophy, and pes cavus; and Bickerstaff,[13] four generations of a family with spastic paraplegia and, in rare instances, retrobulbar neuritis. One of Bickerstaff's family had amyotrophy, and another, congenital diplegia. Schut [14] made a detailed study of a large family in which clinical manifestations of degeneration were highly variable. His was the first genetic study since the reports of Ballet and Rose [15] and Raymond and Rose [16] to show a relationship between spastic paraplegia and hereditary ataxia in the same stock. The family presented here is similar in many respects to that of Schut.

CLINICAL MATERIAL

The family consists of seven generations, with 283 members, 238 of whom were living at the time of the study, in 1949-1950 (Fig. 1). Of the total, 21 have been significantly disabled by progressive neurological disease; of these, 8 were examined by us, and clinical or hospital records of 5 others were secured. All asymptomatic members of the family who were accessible and cooperative were also examined; in particular, all living siblings and children of definitely affected members were seen. Thus, clinical data on a total of 96 members of the family were obtained. Hearsay information was accepted only if agreed upon by several informants. Fourteen members were considered to have preclinical or abortive forms of the disease. Members *I-1* and *I-2* are reported to have died early in adult life on board ship en route to this country in the latter half of the last century. Neither they nor any of their relatives in Germany (Thuringia) are known to have been affected, and, so far as is known, there has been no consanguinity.

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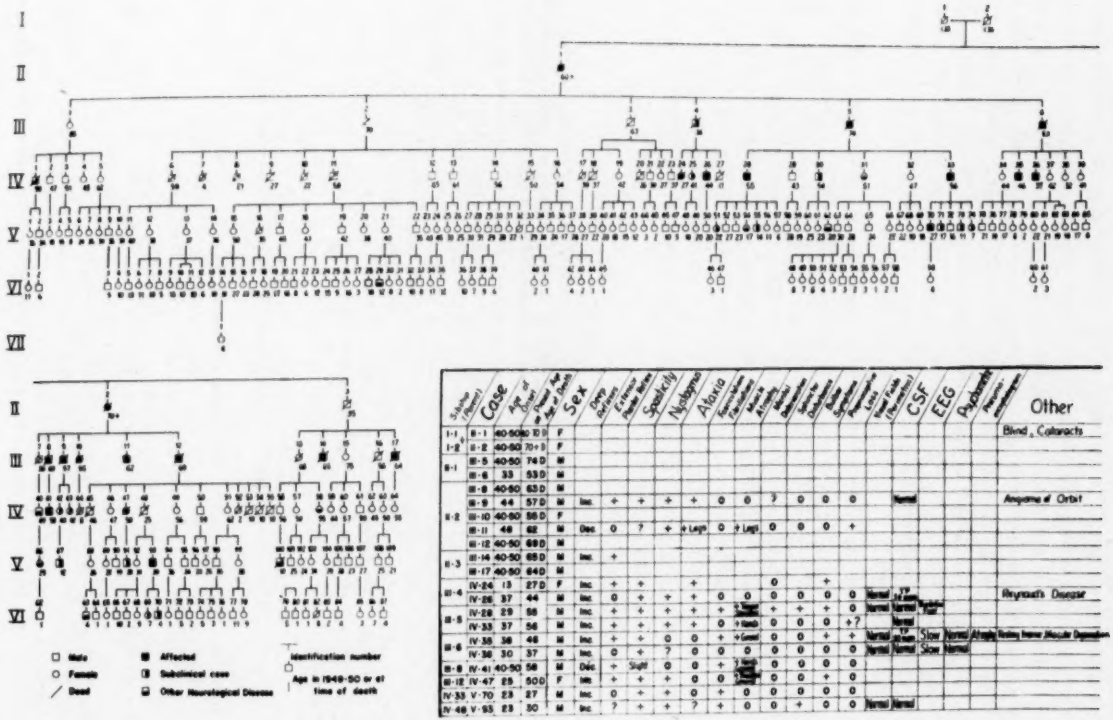

Subclone (Above)	Case	Age at Onset	Duration of Illness & Age at Death	Sex	Deep Reflexes	Extensor Plantar Reflex	Spasticity	Nystagmus	Ataxia	Dysarthria (Scanning)	Tremor & Rigidity	Mental Deterioration	Speech Disturbance	Dysphagia	Sensory Impairment	Loss	Visual Fields (Perimetry)	CSF	EEG	Psychiatric	Other
I-1	II-1	40-50	10 D	F																	Blind, Cataracts
I-2	II-2	40-50	70+ D	F																	
II-1	III-5	40-50	74 D	M																	
	III-6	33	53 D	M																	
II-2	III-8	40-50	63 D	M																	
	III-9	44	57 D	M	Inc.	+	+	+	+	0	0	?	0	0	0		Normal				Anosmia of Orbit
	III-10	40-50	58 D	F																	
	III-11	48	62	M	Dec.	0	?	+	+ Legs	0	+ Legs	0	0	0	+						
	III-12	40-50	69 D	M																	
II-3	III-14	40-50	65 D	M	Inc.	+															
	III-17	40-50	64 D	M																	
	IV-24	13	27 D	F	Inc.	+	+		+			0			+						
II-4	IV-25	37	44	M	Inc.	0	+	+	+	0	0	0	0	0	0	0	Normal	↓ IgG			Reynaud's Disease
	IV-28	29	55	M	Inc.	+	+	+	+	+	+ Tremor	+	+	+	0		Normal	Normal	Mixture		
II-5	IV-33	37	56	M	Inc.	+	+	+	+	0	+ Speech	0	0	0	+	?		Normal			
	IV-35	36	46	M	Inc.	+	+	0	0	+	+ Lower	0	0	+	+		Normal	↑ IgG	Slow	Normal	Ataxia, Tremor, Intent, Absolute Dependence
II-6	IV-38	30	37	M	Inc.	0	+	?	0	0	0	0	0	0	0	0	Normal	Normal	Slow	Normal	
II-8	IV-41	40-50	58	M	Dec.	+	Slight	0	0	+	+ Speech	0	0	0	0						
II-12	IV-47	25	50 D	F	Inc.	+	+	+	0	0	+ Speech	0	0	+	0						
IV-33	V-70	23	27	M	Inc.	0	+	+	0	+	0	0	0	0	0						
IV-48	V-95	23	30	M	Inc.	?	+	+	?	+	0	0	+	0	0	0	Normal	Normal			

Fig. 1.—Genealogical chart of the R. family. The findings in the clinical cases are tabulated; details appear in the text.

The clinical manifestations of degeneration in the central nervous system showed considerable variation; illustrative case histories follow. For convenience, the cases are arbitrarily separated into four groups.

GROUP I

CASE *IV-35.*—This was the first member of the family seen by us. He was admitted to St. Louis City Hospital at the age of 46. There was an eight-year history of progressive stiffness and difficulty in walking. Slurring of speech had been noted for the past year or more. Cramping pains in the legs had been present for several months. Examination revealed no definite nystagmus, although there were slight weakness of upward gaze and some unsteadiness of extraocular movements. For a day following the taking of a pneumoencephalogram there was weakness of convergence. The eyes appeared very prominent, and the expression was fixed. Speech was slurred and irregular but not definitely scanning. There was moderate generalized muscular wasting with questionable fibrillations in the tongue and definite fasciculations in the muscles of both legs. Spasticity was generalized and marked in the lower extremities. The patient could walk with assistance and manifested a spastic-diplegic gait. There was no ataxia. At times a definite pill-rolling tremor of the right hand and forearm was seen. All deep reflexes were hyperactive, including the jaw jerk. There was bilateral sustained ankle clonus with bilateral extensor plantar reflexes. Abdominal and cremasteric reflexes were active. A slight diminution of position sense was found in both lower extremities. Ophthalmological consultation indicated normal visual fields and early macular degeneration bilaterally. Barium

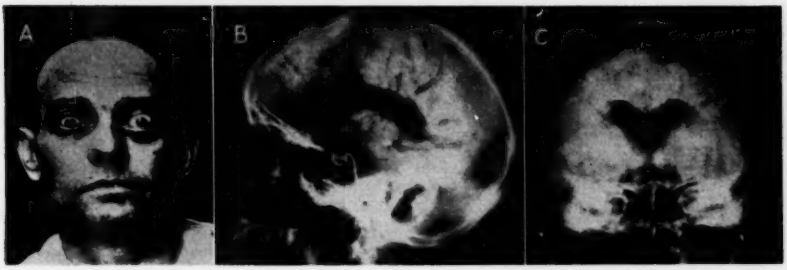

Fig. 2.—*A*, facies in Case *III-9* before operation for removal of angioma of the left orbit. Note the prominence of the right eye, as well as of the left, the staring expression and the frontal baldness. *B* and *C*, pneumoencephalograms in Case *IV-35*, illustrating general ventricular dilatation and increased sulcal markings.

swallow demonstrated some stasis in the lower third of the esophagus with a tortuous and irregular outline and absence of peristalsis. The results of routine laboratory examinations were normal. Lumbar puncture on two occasions yielded cerebrospinal fluid which contained 50 and 31 mg. of protein per 100 cc. and was normal in other respects. The basal metabolic rate was +4%. Psychometric evaluation revealed an intelligence quotient of 102, with no definite evidence of organic brain damage. Electroencephalograms (Fig. 3) revealed a moderate nonfocal, slow dysrhythmia. Routine roentgenograms of the skull were normal, and pneumoencephalography (Fig. 2*B* and *C*) showed generalized ventricular dilatation and exaggerated sulcal markings. The impression was that of diffuse cortical atrophy.

GROUP II

CASE *III-9.*—This patient first noted pain and failing vision in his left eye when he was 44. He was admitted to Barnes Hospital, to the service of Dr. Ernest Sachs, in 1926. Except for the obvious exophthalmos (Fig. 2*A*), physical examination revealed only increased deep reflexes. At operation a well-encapsulated, "typical" angioma was successfully removed from the left retro-orbital space. Routine laboratory studies and roentgenograms of the skull revealed nothing abnormal. During the next 14 yr. he experienced progressive difficulty in the use of his legs

and eventually became confined to a wheel chair. In 1940, at the age of 57, he was admitted to St. Louis City Hospital for removal of nasal polypi, which were obstructing his breathing. He was thought to have some memory defect at that time and was noted to have mild bilateral exophthalmos. There were weakness of lateral gaze in both directions and pronounced nystagmus. Speech was slurred. There was a moderate degree of ataxia with some spasticity. The cremasteric and abdominal reflexes were active; the tendon jerks were all hyperactive, and an extensor plantar reflex was elicited bilaterally. The sensory status was normal. Routine laboratory tests and lumbar puncture gave normal results. The patient died suddenly after operation, of pneumonia. Autopsy revealed no gross abnormality of the brain; microscopic study was unsatisfactory.

CASE *IV-26.*—This patient was well until the age of 37, when he began to have progressive stiffness and awkwardness in his legs. Examination when he was 44 revealed prominent eyes with definite nystagmus on upward and lateral gaze. Speech was irregular and indistinct. There were spasticity and a moderate degree of ataxia in all extremities. All tendon reflexes were hyperactive, with bilateral sustained ankle clonus but normal plantar responses. The jaw jerk was hyperactive, and abdominal and cremasteric reflexes were present. There was no sensory deficit. An eight-year history of sensitivity to cold in the fingers was also elicited. The fingers were cold and of a mottled red color, and the skin at the tips of several fingers was indurated and cracked. The patient had been studied at Barnes Hospital five years previously. The results of routine laboratory tests and of lumbar puncture were normal. The protein content of the fluid was 54 mg. per 100 cc.

GROUP III

CASE *III-11.*—This patient experienced progressive difficulty in walking when he was 48. Examination at the age of 60 revealed prominent nystagmus on gaze in all directions. Speech was slightly slurred, and the tongue deviated slightly to the left. The patient was unable to stand in the Romberg position with the eyes open, and there was some ataxia in the lower extremities but none in the upper. The gait was wide-based, and there was a slight tremor of the head. Moderate difficulty in relaxation was found in all extremities. There was definite atrophy of the leg musculature bilaterally. The biceps and triceps reflexes were hypoactive, and tendon reflexes in the lower extremities were unobtainable. Abdominal and plantar reflexes were normal. There was slight loss of position and vibratory sensation in the lower extremities.

CASE *IV-41.*—This 58-yr.-old patient first noted difficulty in walking during the fifth decade of life. With progression, there has been difficulty in the use of the hands. Examination revealed some mental slowness, which the family said had always been present. There was no nystagmus. The expression was fixed. Speech was slurred, nasal, and rather slow. The gait was wide-based, with some circumduction and a tendency to walk on the lateral margin of the foot. There was slight spasticity. The hands were used awkwardly because of weakness, but there was no ataxia. Definite fibrillations were seen in the tongue, and fasciculations were generalized. There was some general muscular atrophy, being rather pronounced in the intrinsic muscles of the right hand and, to a less extent, in the left hand. Tendon reflexes were normal in the upper extremities, but were absent in the lower extremities. Abdominal and cremasteric reflexes were active, and extensor plantar reflexes were elicited bilaterally. Sensory examination showed an essentially normal status.

GROUP IV

CASE *IV-24.*—This patient, the sister of *IV-26*, first noted awkwardness in gait when she was 13 yr. old. She had "weak" ankles and tended to fall frequently. The difficulty progressed, and speech began to become indistinct and slurred when she was about 18. When she was 22, in 1930, she was seen by a neurologist, who made a diagnosis of "spastic spinal paralysis." It was thought that she did not have pes cavus. The upper extremities became unsteady in the next two years; bulbar symptoms became severer, and the patient died of a respiratory infection when she was 27.

In subjects of Group I pyramidal-system disease predominated, with occasional evidence of more widespread degeneration, the disease becoming clinically evident in adult life. The disease in Group II differed only in that a prominent component

of cerebellar symptoms was admixed with the spasticity (hereditary spastic ataxia). The disorders in Group III were manifest amyotrophies of adult life; the condition in Case *IV-41* was indistinguishable clinically from amyotrophic lateral sclerosis. The muscular atrophy, confined to the legs, in *III-11* was suggestive of the Charcot-Marie-Tooth syndrome. Precocious onset in adolescence and rapid progression, culminating in death from bulbar involvement, distinguished the case in Group IV; our information on the clinical status was second-hand and incomplete, however. The data in the tabular material presented in Figure 1 emphasize the overlap of symptoms in our cases, as compared with the "pure" classic symptoms of hereditary degenerative disease.

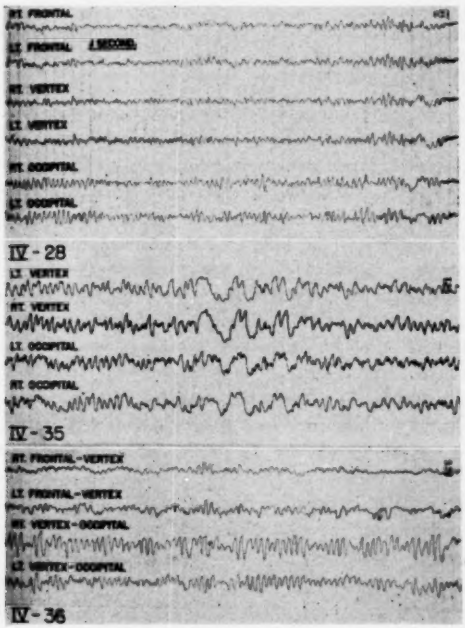

Fig. 3.—Electroencephalographic tracings, showing borderline fast dysrhythmia in Case *IV-28*, and slow dysrhythmias in the brothers *IV-35* and *IV-36*.

We observed in many of the patients afflicted with the major clinical syndrome a characteristic facies (Fig. 2*A*). This was also noted by Schut.[14] The soft tissues were spare, and the expression tended to remain fixed. The eyes were very prominent, and a receding frontal hair line was often noted. A high-arched palate was sometimes observed.

Routine laboratory studies were essentially noncontributory. Negative serological reactions for syphilis were reported in 11 cases. The basal metabolic rates were normal in three cases. The spinal fluid was examined in seven cases and was entirely normal except for doubtfully significant protein values of 50 and 54 mg. per 100 cc. in two cases. Psychometric examination demonstrated no deterioration

in two patients. The electroencephalogram showed slow dysrhythmias in two subjects and a borderline fast dysrhythmia in another (Fig. 3). A pneumoencephalogram in Case *IV-35* revealed diffuse cortical atrophy with general dilatation of the ventricles (Fig. 2*B*, *C*).

Fourteen subjects without complaints were considered to have abortive or preclinical forms of the disease.

Member *III-4* was never disabled, but several members of the family agreed that he "didn't walk right." *IV-30* had definite nystagmus on lateral and upward gaze, a slightly wide-based gait, and mild hypotonia of the upper extremities. The jaw jerk was hyperactive; the tendon jerks were normal. Abdominal and cremasteric reflexes were active; plantar reflexes were extensor. *V-71* had definite fasciculations in both calves and hyperactive tendon reflexes. The right pupil was larger than the left, although both reacted well to light and in accommodation. All the other patients in this group had nystagmus, usually manifest upon upward, as well as lateral, gaze. Other findings included unequal pupils (*V-51*), increased tendon jerks (*IV-43*, *V-73*, *V-91*), and asymmetry in movements for the face and palate (*V-91*).

Apparently unrelated clinical neurological disease was also found in 10 members of the family. Other cases were probably missed, since less cooperation and detailed information were secured from the branches of the family which were free of the primary clinical disease. Indeed, frank opposition to the investigation, with denial of a "taint," was often met.

Included in this group are the following disorders: progressive presenile mental deterioration with paralysis (*IV-1*), chorioretinitis (*IV-31*, *IV-40*), diabetic neuropathy and hemorrhagic retinopathy (*IV-58*), "encephalitis" with residual hemiparesis and convulsions (*V-54*), "encephalitis" with dementia (*VI-29*), nonprogressive congenital diplegia (Little's disease) with strabismus (*V-62*),[17] congenital diplegia with imbecility and convulsions (*V-100*), convulsive disorder (*VI-63*), and acute unilateral retrobulbar neuritis with residual atrophy (*V-86*). In the patients afflicted with the principal disease, associated findings were an orbital angioma (*III-9*), Raynaud's disease (*VI-26*), and macular degeneration of the retina (*IV-35*).

Whereas the principal degenerative disease, clinical or subclinical, appears to be inherited as a dominant characteristic, the other neurological disorders had a more random distribution in the family.

COMMENT

The most striking feature of the clinical cases in this family is the variable degree of overlap of symptoms referable to the degeneration of pyramidal, cerebellar, and striatal systems and of the anterior-horn cells. However, pyramidal symptoms were the most uniformly observed. The unusual facies was not constant. The course in all cases was one of progressive motor impairment, always with some speech involvement. In the majority of cases the life span did not appear to be significantly affected unless bulbar involvement became severe (*IV-24*, *IV-47*).

Nystagmus was seen frequently and early (Bell and Carmichael[6]). Cramping pains were reported in the legs in one patient (*IV-35*) and in the flank in another (*IV-28*). Sensory disturbances were minimal in three patients. Urinary and fecal incontinence developed in *IV-28*, and fecal urgency, in *V-93*. Symptoms and signs of optic nerve atrophy were not associated with the major symptoms. Members

17. Since *V-62* is the child of a member with definite subclinical disease, *IV-30*, his condition may well be considered as a variant of the major syndrome.

II-1 and *III-1* were blind, but both had cataracts. Retinal macular degeneration was observed in *IV-35*, and an isolated optic neuritis with residual atrophy was seen in *V-86*.

The available electroencephalogic and pneumoencephalographic findings indicate that the degenerative process may be considerably more generalized than is evident from findings at neurological examination (cf. the pathological observations of Paskind and Stone [4] and Andre-van Leeuwen and van Bogart [11]). Mental deterioration was uncommon, and no obvious psychiatric abnormalities were observed in any member of the family.

In several of the subjects of this study the disease had been diagnosed by competent examiners as Erb's syphilitic paraplegia, amyotrophic lateral sclerosis, combined sclerosis, and multiple sclerosis. The variety of clinical manifestations in this family emphasizes the importance of a detailed family history in isolated cases of degenerative disease of the nervous system, however closely the clinical picture simulates nonhereditary disease.

The classification of some members of the family as having preclinical cases of the disease appears entirely justified by comparison of their minimal symptoms with those of the manifest syndrome. The fact that all these members were offspring of affected or potentially affected parents is confirmatory. Whether all patients with clinical disease may be expected to show signs at an early age, however, is not established. Case *III-9*, in which the neurological status was said to be normal by a very competent observer in the year of onset of motor symptoms, indicates that preclinical signs are not constantly present.[18]

Both the variety of manifestation of the major syndrome and the prominence of other types of neurological disorder indicate that there is probably a general factor of neural vulnerability present to varying degrees in all members of the family, and relatively independent of the dominantly inherited degeneration of the central nervous system. More than 4% of the family had neurological disease which differed from the primary entity.

The inheritance in this family evidently follows a dominant pattern. The only members with clinical disease who did not have an affected parent were the offspring of *II-2* and *IV-48*. Member *II-2* died in an accident, and, *IV-48*, of intercurrent infection at ages when clinical symptoms would not be expected to be manifest. It does not appear necessary to postulate a suppressing action of a gene. An unusual feature (Bell and Carmichael [6]) of this family is the significant tendency toward sex-linkage. Sixteen of 21 of the members with clinical disease and 8 of 14 of the members with subclinical disease were males, as were the two transmitters who died before symptoms developed. Of these 37 subjects, 70% were males. There were 137 males and 146 females in the entire family. This total sex ratio (48.4% males to 51.6% females) suggests, although the variation from the general population is probably not statistically significant, that in some cases the gene complex may be lethal to males.

The tabular material in Figure 1 illustrates that there is a tendency for symptoms to become manifest at an earlier age in the later generations (Bell and Carmichael,[6] Schut [14]). This tendency appears to be more definite than can be accounted for on

18. In Case *IV-39* diplopia and sustained nystagmus on lateral and upward gaze have developed since this paper was submitted for publication.

the basis of the earlier recognition of symptoms in a family that is alerted to them. In a particular sibship, there appears to be some consistency in age of onset, but exceptions are not infrequent (*III-5* and *III-6; IV-24* and *IV-26*). In three sibships (*III-4, III-5, III-6*), for whom the date of onset was most definitely established, the onset in the older sib occurred at an older age; Bell and Carmichael reported that this variation is a frequent occurrence. There did appear to be less variation in the clinical picture among siblings than among more distant relations.

It appears certain that the phenotypic inconstancy is to a large extent determined by genetic interactions, resulting in the various clinical mosaics discussed by André-van Leeuwen and van Bogaert.[11] It should be emphasized, however, that there is undoubtedly a large component of biological variation which is not demonstrably of genetic origin. It is rather assumed in many clinical-genetic studies of hereditary disease that the age of onset and the locus of degeneration are determined by genetic factors acting upon a constant substrate. However, numerous observations in experimental genetics oppose such an assumption; and trauma, pregnancy, acute disease, and emotional stress are commonly described by patients as precipitating factors in the development of symptoms of hereditary disease. Moreover, the variation in age of onset of symptoms with birth order is difficult to explain genetically. It does not appear to be biologically justifiable to overlook any factor, acute or chronic, which may affect the nutrition and metabolism of genetically poorly endowed tissues, and it is evident that cell environmental factors begin to operate at the time of conception. The possibility of effective therapy lies only in the understanding of the essential metabolic failings that lead to cell decay.

SUMMARY

A dominantly inherited degenerative disease of the central nervous system was studied in seven generations of a family having 283 members. The variety of findings among the 21 clinically affected members is pointed out. The pyramidal system was involved most prominently, but cerebellar, lower motor neuron, and extrapyramidal lesions were admixed, in multiple combinations. The presence among other members of the family of subclinical manifestations and the presence of apparently unrelated disease of the nervous system are noted.

It is believed that a single dominant gene in association with modifiers is largely responsible for the various phenotypic patterns. The predominant incidence of the disease among males indicates partial sex-linkage in either the main gene or the modifiers.

The clinical and genetic features of this family are discussed, and it is pointed out that it is biologically unsound to ascribe all variable clinical findings to genetic factors alone.

Mr. Joseph Inukai assisted in preparing the illustrations.

PATTERNS IN PERCEPTION ON SIMULTANEOUS TESTS OF FACE AND HAND

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PREVIOUSLY it was shown that examination of the cutaneous modalities by the method of double simultaneous stimulation elicited defects in perception which were not apparent on single stimulation. The defects, described as "extinction," "obscuration," "displacement," and "allesthesia," were observed in groups of patients with localized or diffuse disease of the central nervous system.[1] In each group the defects in cutaneous perception obtained on double simultaneous stimulation were most apparent in the hand and least in the face. The object of the present investigation was to determine the patterns of responses in normal subjects, adults and children to simultaneous stimulation of the face and hand—the "face-hand" test.[2] The observations on this normal group were then compared to some extent with the responses of patients with organic mental syndromes, aphasia, and schizophrenia.

MATERIAL

The "normal" subjects were children and adults. These subjects were persons attending hospital clinics in whom there was no evidence of disease of the brain, and school children, staff personnel, and students, in whom there was no manifest disorder of the central nervous system. None of them had been examined previously by the method of double simultaneous stimulation.

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1. (*a*) Bender, M. B., and Furlow, L. T.: Phenomenon of Visual Extinction in Homonymous Fields and Psychologic Principles Involved, Arch. Neurol. & Psychiat. **53**:29-33 (Jan.) 1945. (*b*) Bender, M. B.: Extinction and Precipitation of Cutaneous Sensations, ibid. **54**:1-9 (July) 1945; (*c*) The Phenomenon of Sensory Displacement, ibid. **65**:607-621 (May) 1951. (*d*) Bender, M. B.; Shapiro, M. F., and Schappell, A. W.: Extinction Phenomena in Hemiplegia, ibid. **62**:717-724 (Dec.) 1949. (*e*) Bender, M. B.; Wortis, S. B., and Cramer, J.: Organic Mental Syndrome with Phenomena of Extinction and Allesthesia, ibid. **59**:273-291 (March) 1948. (*f*) Bender, M. B.; Shapiro, M. F., and Teuber, H. L.: Allesthesia and Disturbance of Body Scheme, ibid. **62**:222-231 (Aug.) 1949. (*g*) Bender, M. B., and Nathanson, M.: Patterns in Allesthesia and Their Relation to Disorder of Body Scheme and Other Sensory Phenomena, ibid. **64**:501-515 (Oct.) 1950.

2. Bender, M. B.; Fink, M., and Green, M.: Patterns in Perception on Simultaneous Tests of the Face and Hand, Tr. Am. Neurol. A. **75**:250-252, 1950.

The subjects were divided into three groups according to age: children of 3 to 6, and 7 to 12 yr., and "adults" over 12 yr. of age.

For comparison with the normal group, we studied patients in the wards of the Bellevue Psychiatric Hospital. They were divided into three groups on the basis of their disease—schizophrenia, organic psychoses, and aphasia. No attempt was made to study separately the clinical types of schizophrenia. Most of the patients had the paranoid, mixed, or simple variety of schizophrenia. The patients with organic mental changes showed defects in memory, orientation, and calculation, as well as other signs and symptoms characteristic of diffuse disease of the brain. The clinical diagnoses for most of these patients was Alzheimer's' disease, arteriosclerotic encephalopathy, severe cerebral trauma, brain tumor, or toxic encephalopathy. The subjects with aphasia were those who showed characteristic difficulties in communication. Those who had concomitant hemiparesis or a hemisensory defect noticeable on single stimulation were not included in this series.

METHOD

The subject was instructed to close the eyes. When this was done, the face (cheek) and either the ipsilateral or the contralateral hand (any part of the hand or digits) were simultaneously touched or stroked with the examiner's fingers. The subjects reported either one or two sensations. When only one percept was reported, the subject was asked if there was still another and, if so, to indicate its location and quality.

After the initial trial, in each subject, the opposite cheek and hand were stimulated in the same manner. These tests were repeated and the results recorded, until the subjects consistently reported both stimuli correctly. In those subjects who failed to localize the two stimuli correctly after six or eight trials, other parts of the body were tested in such combinations as face-face, hand-hand, face-breast, or penis-hand, these stimulations alternating with the face-hand test.

In a second, separate series of studies, pinprick stimuli were used in a similar fashion. In both series, care was taken to apply the stimuli at the same time and with the same intensity. It was apparent that subjects who made consistent errors in reporting would be correct as soon as the stimuli were applied consecutively rather than simultaneously, even if the time lag between stimuli was that of one or two moments. It was also necessary to use naive normal subjects, since subjects previously tested did not show the patterns noted below.

RESULTS

The responses obtained on the face-hand test fell into four groups: (*a*) a touch sensation on the face and the hand, indicating the correct and expected perception; (*b*) a touch sensation on the face only, implying no sensation in the hand; (*c*) a touch sensation on both sides of the face, and (*d*) a touch sensation on the hand only, implying none on the face. When only one stimulus was reported, the subject was asked if there was any other sensation. The occasional reply was that there was another percept, and the subject correctly pointed to the second locus. Many subjects, however, reported that they had not perceived another stimulus, usually adding the statement: "I was not paying attention; do it again," or, "I'm not sure; maybe it was somewhere over here," and pointing in the direction of the side of the body of the poorly felt stimulus. In some instances, while correctly localizing the second percept, they volunteered the statement: "It was not as strong as the other one," or "It doesn't seem as sharp."

Before we proceed with the results, we must define the special terms used. In other communications the failure of the subject to report one of two simultaneously applied stimuli has been called "the phenomenon of sensory extinction," or "extinction."[1a, b] The part of the body where the stimulus was perceived is said to be "dominant" to the part of the body where the simultaneous stimulus was not perceived, or perceived faintly. The latter diminution in the quality of a sensation was

termed "obscuration." When the subject reported two sensations, but mislocalized one of them, the "displacement" of a percept is said to have occurred.[1e] Displacements are usually in the direction of the dominant stimulus and may be partial or complete. The displacements noted in this series were from the hand to the cheek of the same side. Rarely did the displacements occur to the neck or shoulder.

Initial Trial.—The results were analyzed from the standpoint of initial and subsequent trials. On the initial trial of the face-hand test with touch stimulation in normal subjects, face dominance was apparent in all age groups. More than half of such normal adults reported the sensation in the face and none in the hand. Three subjects mislocalized the sensation in the hand to the face. In the groups of normal children, 90% under the age of 6 yr. reported only the face percept or mislocalized the hand percept to the face. This pattern of face dominance is also seen in the children from 7 to 12 yr. of age, but to a less extent.

Of the normal subjects, five adults reported the hand stimulation only on the initial trial. No example of displacement from face to hand was noted.

This pattern of face dominance by hand extinction or by displacement of the hand percept to the face was even more apparent in the patients examined. It was most evident in patients with organic mental changes, 93% of whom did not report

TABLE 1.—*Response to Touch Stimulation on Initial Trial*

	Total	Correct Responses	Face Only	Face-Face	Hand Only
Normal adult	160	77	75	3	5
Normal child, 3-6 yr.	56	10	28	18	0
Normal child, 7-12 yr.	76	38	27	9	2
Schizophrenia (unclassified)	74	26	45	1	2
Organic mental syndrome	120	9	94	14	3
Aphasia	23	12	11	0	0

both stimuli correctly. In examinations of schizophrenic subjects and patients with aphasia, responses similar to those of the normal adult were observed in the initial trial.

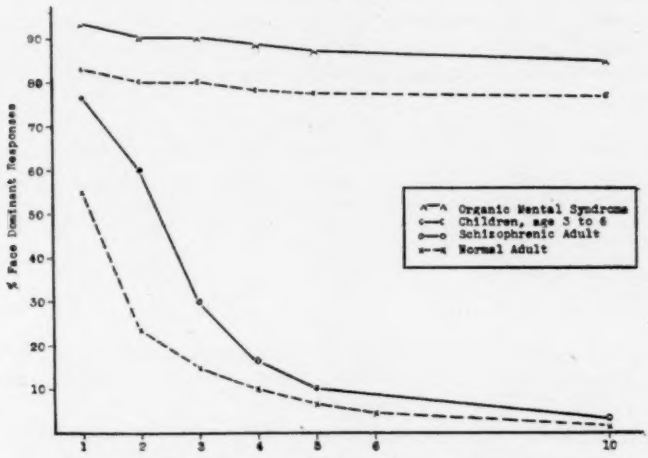
Hand dominance was occasionally seen in the patient and rarely in the normal subject. In cases of hand dominance the subject reported the hand, but not the face, percept. It was seen in the initial trial in five normal adults. These subjects reported both stimuli correctly on subsequent testing. In the patients with organic mental changes hand dominance was an inconstant response, and repeated testing the same day, or on subsequent days, demonstrated the more usual persistent pattern of face dominance.

Subsequent Trials.—Of the 83 normal adults who made errors on the initial trial, 43 made correct responses on the second trial and 12 on the third trial. In a few subjects, four, five, or six trials were necessary before the two stimuli were correctly localized. These subjects were assumed to be normal, although complete psychological tests were not made. It was noted that anxiety (tension during examination or a strong desire to please) interfered with the early correct recognition of the stimuli. In all normal subjects, including those with anxiety, once the correct response was obtained (even after many trials with errors), it was elicited on all subsequent testing. It seemed as though a number of trials was necessary for

the subject to get into the "set" of the examination, and that, once in the set, he reported the stimuli accurately, even after the lapse of many days.

In testing the normal young child, it was apparent that in most cases many trials were necessary before the correct response was consistently elicited. Also, the child did not always give a correct response on subsequent testing. Repeated testing over many days, however, elicited the same patterns of face dominance. This was noted in 36 of the 56 children tested. In a number of instances the child watched the application of the stimuli and thus reported the perceptions correctly. But as soon as the test was repeated with the eyes closed, the child again reported only one stimulus. It was evident that the child could not get into the "set" of the examination, even with visual cues.

This difficulty was not very apparent in all children. In the older group (ages 7 to 12 yr.) only 17 of the 76 failed to give the correct response after the initial few trials.



Responses to face-hand test on initial and subsequent trials.

The responses obtained on repeated trials of the face-hand tests in normal subjects also followed a consistent pattern. As on the initial trial, face dominance was prevalent in all subjects. It was manifest either by (*a*) extinction or obscuration of hand stimuli or (*b*) displacement of hand stimuli to the face, or, in several instances, in a direction toward the face.

In contrast to normal adults, patients with organic mental changes were unable to report the two stimuli correctly, even after many trials. When the patient reported the percept in one test correctly, he frequently failed on subsequent testing. It was also apparent that testing on subsequent days still elicited displacement and extinction of stimuli. This is in strong contrast to the responses of apparently normal subjects, who seldom made an error on subsequent trials, days after the initial examination. The responses obtained in this group demonstrated the patterns of face dominance in most of the tests. Displacement of the hand percept to

the face was frequent. In some instances displacement or extinction was present despite the fact that the patient watched the application of the stimuli to the face and hand. Extinction was very common on homolateral or heterologous testing, while displacement was apparent mostly on heterologous testing.

The schizophrenic and the aphasic patients gave reports which were similar to those of normal adults. After the first two trials percentage of error in hand sensation was slightly higher than in the normal group. Persistent bizarre responses were elicited from a number of the schizophrenic subjects. These reports included multiple responses to single or double stimuli, persistent displacements to one area from any other body area, and mirror reversals of localization. These were inconsistent during an examination and from day to day. As with the normal adults, testing the schizophrenic or aphasic subject on consecutive days failed to elicit extinction phenomena once the test had accurately been reported before.

A comparison of the responses of each of these groups to multiple testing is shown in the accompanying chart.

Pinprick Stimulation.—It is known that the type of stimulus applied influences the results in perception. To demonstrate the importance of this factor, similar groups of subjects were tested using two pinprick stimuli instead of two touch

TABLE 2.—*Response to Pinprick Stimulation on Initial Trial*

	Total	Correct Responses	Face Only	Face-Face	Hand Only
Normal adult	68	51	15	2	0
Normal child, 3-6 yr.	45	16	26	2	1
Normal child, 7-12 yr.	39	25	14	0	0
Schizophrenia	50	36	13	0	1
Organic mental syndrome	49	9	33	3	2

stimuli. With pinprick stimulation of the face and hand, face dominance was again manifest in all the groups. However, the incidence of error in perception of the pinprick in the hand was lower than that with a touch stimulus. The results are recorded in Table 2.

Repeated testing with two pins in the normal adult subjects elicited the correct responses in the intial three trials. Fewer of the children failed to report the test accurately after the initial trials. It was possible in a number of instances to alternate touch and pinprick stimulations and to demonstrate extinction to touch, but correct localization to pinprick. Moreover, with more intense pinprick stimulation, extinction and displacement were less frequently observed.

These phenomena, namely, extinction and displacement, were even more apparent in the patients with organic mental syndromes. Displacement of touch stimulation could be alternated with correct localization of pinprick stimulation. A combination of touch to the face and pinprick to the hand evinced the combination of displacement and obscuration, as the patient reported "a touch on the face, and a dull one on the other side (of the face)." Pinprick to the cheek and touch to the hand resulted in extinction of the hand percept, or, occasionally, the report of a pinprick on both the cheek and the hand.

The schizophrenic subjects were able to localize the pinprick stimulus accurately after the initial few trials, as had the normal adults.

COMMENT

By using the method of double simultaneous stimulation in tests of the face and the hand, a consistent pattern of responses has been observed in a variety of subjects. The stimulus to the face is more readily perceived than the one to the hand. Moreover, the face percept influences the hand percept, frequently causing the displacement of sensation. This pattern of responses has been repeatedly demonstrated in both the normal and the abnormal subjects and is manifest in extinction, obscuration, and displacement. Extinction is most, and displacement is least, frequent. In extinction, the face percept is correctly reported as to quality and locus, but the hand stimulus is not perceived at all. In all the foregoing tests of patient or normal subjects, whether the responses were accurate or not, it was noted that the subject almost invariably pointed to the face stimulus first. Occasionally the hand percept was perceived and correctly localized, but assumed a qualitative difference, always of diminution. In displacement the stimulus to the hand was mislocalized to the face, or in the direction of the face, e. g., to the shoulder or neck. In some instances if the face and the hand of the same side were stimulated, the subject occasionally reported two sensations in the face. None of these phenomena was haphazard. While the frequency with which any one of these effects was observed might be affected by attention, drugs, or variation in stimuli, its pattern was consistent.

These responses to the face-hand test are modified by many factors. Some of the influencing factors are (*a*) attention, (*b*) age of subject, (*c*) simultaneity of stimuli, (*d*) type of stimulus, (*e*) strength of stimulus, (*f*) locus of stimulation, and (*g*) internal state of organism. These factors may alter the frequency with which extinction and displacement appear, but they do not change the pattern of face dominance.

The subject's awareness of the test is a major factor in the appearance of the phenomenon of extinction. Both attention and previous experience can bring stimuli to awareness. In a series of 20 adults who were informed that two stimuli were to be applied, none showed extinction of percepts. Because previous experience can influence a response, it was necessary to record the findings on initial trial in naïve subjects. By this method the factor of previous experience was minimized. At the same time, the subject was not apt to be on the "alert" for the number of stimuli he was to receive. Consequently, one might say that the reason the subject perceived only one stimulus, or perceived one stimulus and displaced the percept of the other, is that he was not paying attention.[3] This criticism may be valid, but the significant fact is that the error was always made in the hand and not in the face. If it were mere inattention, one would expect 50% of the single responses to double simultaneous stimulation to be in the hand and 50% in the face. But this type of chance error was not observed. Of the single responses to double simultaneous stimulation, 95% were of the face percept and 5% of the hand percept. This pattern of face dominance or hand extinction was further established during subsequent examinations. Moreover, when displacement was seen in normal subjects, it was to the face and not to the hand.

This pattern of face dominance to double simultaneous stimulation was found to be exaggerated in normal young children, of whom 83% demonstrated either hand extinction or displacement of the hand percept to the face on the initial trial.

3. Critchley, M.: The Phenomenon of Tactile Inattention with Special Reference to Parietal Lesions, Brain **72**:538-561, 1949.

Moreover, this high percentage of responses of face dominance persisted on subsequent trials. In the older children, also, face dominance was consistently demonstrable. It was noted that the younger the child, the more distinct was this pattern of face dominance.

Hand extinction might be attributed to an inability to perceive two stimuli at once. This particular defect has been noted in patients with severe mental changes by Goldstein.[4] However, in patients with severe mental changes or in young children stimuli applied to both cheeks, or both hands, or any other two homologous body areas were correctly reported as two sensations. There was neither extinction nor displacement. Goldstein's observation, therefore, cannot be used as an explanation of hand extinction.

It is noted that face dominance was apparent no matter what type of stimulation was used. Simultaneous pinprick stimulations revealed the pattern of face dominance, although with a lower frequency than touch stimulations. Other cutaneous stimulation, such as application of two tuning forks or hot and cold tubes, repetitive rubbing, and repetitive pinprick stimulation, was used, and face dominance was manifest regardless of the cutaneous stimulation employed.

The importance of the simultaneity of the stimuli has already been alluded to. In subjects in whom extinction was persistent, consecutive application of the stimuli invariably resulted in the perception of two stimuli. In normal adults consecutive stimulation of the face and the hand, even on the initial trial, never resulted in extinction.

In these studies the stimuli were of equal intensity. This factor was important in eliciting the pattern in the normal subject, for unequal stimuli were seemingly more readily perceived than equal stimuli. After the first few trials the subject was able to perceive the two stimuli, even if one was painful and the other not. In patients with organic mental changes, however, extinction and displacement were manifest despite a wide discrepancy in the quality of the stimuli. By altering the strength of the stimuli, it was possible to alter the response from extinction of the hand percept (if the hand stimulus was weak) to displacement to the cheek (if the hand stimulus was strong). The change from extinction to displacement was also elicited by altering the quality of the stimuli, that is, from touch to pinprick. Nevertheless, the pattern of face dominance was always apparent.

The parts of the body being simultaneously stimulated is another consideration in studying these patterns. We have already alluded to the fact that extinction is commonest in the hand and least in the face. In testing other body areas, the incidence of extinction and displacement is less than in testing the face and the hand. That is, testing shoulder and thigh may not elicit extinction or obscuration, whereas the face-hand test may. Also, in patients with lesions of the brain or spinal cord, the pattern of relation of the body parts to simultaneous stimulation may be altered in a characteristic hemisensory or "level-lesion" syndrome. Further studies are necessary before the significance of the pattern can be interpreted. Any deduction made at this time would be purely speculative. For instance, nothing is gained by stating that face dominance implies a rostral order of sensory dominance.[5] Such a

4. Goldstein, K.:: The Mental Changes Due to Frontal Lobe Damage, J. Psychol. **17**:187, 1944.

5. Cohn, R., and Raines, G. N.: On Certain Aspects of the Sensory Organization of the Human Brain: A Study in Rostral Dominance as Determined by Ipsilateral Simultaneous Stimulation, Tr. Am. Neurol. A. **74**:162-168, 1949.

hypothesis is contradicted by at least one fact, namely, the observation that when the hand and foot are stimulated simultaneously the foot dominates over the hand. Perhaps after more data are accumulated a satisfactory theory may be obtained.

SUMMARY

A pattern in perception in tests of stimulation of the face and hand has been elicited in normal and abnormal subjects by the method of double simultaneous stimulation of cutaneous modalities.

Face dominance, manifest by extinction of the hand percept or by displacement of the hand percept to the face, is seen as a normal phenomenon, manifested in the normal adults and in the patients with schizophrenia and aphasia examined in the series. It is exaggerated in young children and in patients with diffuse disease of the brain, in whom extinction and displacement are persistent after multiple trials.

This pattern of face dominance is manifest regardless of the cutaneous modality tested, there being a change only in the frequency of extinction with change in type of stimulus.

CAPILLAROSCOPIC STUDIES IN CASES OF MULTIPLE SCLEROSIS AND OTHER NEUROPSYCHIATRIC DISORDERS

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THE PURPOSE of this paper is to put on record the observations on capillaroscopic changes in multiple sclerosis and various neuropsychiatric disorders.

A number of articles on the alterations in the capillaries in thromboangiitis obliterans,[1] Raynaud's disease,[2] epilepsy,[3] migraine,[4] neurosis,[3b] nerve injuries, acrocyanosis and hemiplegia,[6] schizophrenia and manic-depressive psychosis,[7] and other mental diseases [8] have been published. Besides the publications of Benedict [9] and Brickner and Franklin,[10] who emphasized spasmodic obliteration of retinal circulation, there exist only two papers, those by Gomirato [11] and by Chiavacci and Putnam,[12] on capillaroscopic observations in multiple sclerosis. The authors of these two papers have studied the capillaroscopic changes in cases of multiple sclerosis, and the incidences of abnormality are closely comparable in the two series.

Read before at the Eleventh Annual Session of the Gülhane Military Medical Academy, May 27, 1950.

From the Department of Neuro-Psychiatry of the Ankara University and Gülhane Military Medical Academy (Prof. R. Adasal).

1. Jahsman, W. E.; Durham, R. H., and Dallis, N. P.: Recognition of Incipient Thromboangiitis Obliterans in Young Draftees, Ann. Int. Med. **18**:164 (Feb.) 1943.

2. Deutsch, F.: Capillary Studies in Raynaud's Disease, J. Lab. & Clin. Med. **26**:1729 (Aug.) 1941.

3. (*a*) Paskind, H. A., and Brown, M.: Constitutional Differences Between Deteriorated and Nondeteriorated Patients with Epilepsy: Capillaries of the Finger Nail Fold, Arch. Neurol. & Psychiat. **49**:49 (Jan.) 1943. (*b*) Hauptmann, A.: Capillaries in the Finger Nail Fold in Patients with Neurosis, Epilepsy and Migraine, ibid. **56**:631 (Dec.) 1946.

4. Redisch, W., and Pelzer, R. H.: Capillary Studies in Migraine: Effect of Ergotamine Tartrate and Water Diuresis, Am. Heart J. **26**:598 (Nov.) 1943.

5. Footnote deleted.

6. Marinesco, G., and Bruch, A.: Recherches de capillaroscopie et des troubles vasculaires dans quelques maladies nerveuses et des glandes à sécrétion interne, Presse méd. **38**:665 (May 17) 1930.

7. Hauptmann, A., and Myerson, A.: Studies of Finger Capillaries in Schizophrenia and Manic-Depressive Psychoses, J. Nerv. & Ment. Dis. **108**:91 (Aug.) 1948.

8. Moragas, J.: La imagen capilar in psiquiatria, Med. clín. **3**:404 (Nov.) 1944.

9. Benedict, W. L.: Multiple Sclerosis as Etiologic Factor in Retrobulbar Neuritis, Arch. Ophth. **28**:988 (Dec.) 1942.

10. Brickner, R. M., and Franklin, C. R.: Visible Retinal Arteriolar Spasm Associated with Multiple Sclerosis: Preliminary Report, Arch. Neurol. & Psychiat. **51**:573 (June) 1944.

11. Gomirato, G.: Alterazioni dei capillari in malati di sclerosi multipla e loro significato, Riv. pat. nerv. **53**:148 (Jan.-Feb.) 1939.

12. Chiavacci, L. V., and Putnam, T. J.: Capillaroscopic Observations in Cases of Multiple Sclerosis, Arch. Neurol. & Psychiat. **61**:577 (May) 1949.

Chiavacci and Putnam [12] observed definite alteration in the capillaries, consisting mainly in spasticity, sluggishness or absence of circulation, and thickening of the intermediate parts of the loop, pointing to the primary nature of vascular changes in the disease. They concluded that these vascular evidences are helpful in the diagnosis of multiple sclerosis.

Capillaries of four patients with multiple sclerosis.

PRESENT INVESTIGATION

Material and Methods.—I have made observations on 21 patients with multiple sclerosis, 380 patients with various neuropsychiatric diseases, and 50 normal persons. In this study I used an ordinary microscope with a magnification of 135, concentric electric illumination, and application of cedar oil, to make the skin more transparent. The nail bed of the fourth finger of each hand was taken under observation on certain times and in a dark room, without squeezing it.

Observations.—The following alterations were observed in cases of multiple sclerosis.

1. Capillary pattern. The horizontal line at the extreme end was rather regular in 17 cases, but it was completely irregular in the remaining four cases. In seven cases the length of capillaries was normal; in 6 all were very small, and in the other 8 cases normal and small capillaries occurred together, the latter being in the majority. In only four cases were there very long capillaries, which were scattered.

In 8 cases of multiple sclerosis all capillaries were very thin; in only 1 case were they thick, and in the remaining 12 cases there was a combination of thin and normal capillaries, with a predominance of the former type. Tortuosity was of normal degree (+) in seven cases and slightly increased in 14 cases.

TABLE 1.—*Abnormalities in Capillary Pattern in the Nail Bed in Twenty-One Cases of Multiple Sclerosis*

Case No.	Sex	No. of Capillaries	Size of Loops: Length			Size of Loops: Thickness			Spasticity	Fragmentation	Thickening of the Intermediate Portion	Tortuosity	Venous Plexus	Circulation
			Long	Normal	Short	Thin	Normal	Thick						
1	M	8	..	8	..	6	2	..	+++	+	4	++	..	+
2	F	10	..	..	10	10	..	..	+++	++	..	+	..	+
3	M	14	4	10	..	2	8	1	—	—	2	++	..	+
4	M	11	..	11	..	2	7	2	+	+	6	+	..	—
5	M	9	..	3	6	4	5	..	—	—	2	+	..	+
6	M	12	..	..	12	12	..	..	+++	++	4	++	..	—
7	M	6	..	..	6	6	..	..	+++	—	..	++	..	+
8	M	15	2	5	8	8	7	..	+++	—	5	++	..	+
9	M	19	4	15	..	13	6	..	+++	+	7	++	..	+
10	M	7	..	7	..	2	5	..	—	+	3	++	..	+
11	M	14	..	4	10	11	3	..	++	+	4	+	..	+
12	M	6	..	6	..	..	..	6	—	—	4	++	..	+
13	M	7	..	..	7	7	..	..	+++	—	1	+	..	+
14	F	8	..	..	8	8	..	..	+++	—	2	++++	..	+
15	M	11	1	7	3	6	5	..	+++	++	4	++++	..	+
16	M	5	..	..	5	5	..	..	+++	—	..	+	..	—
17	M	2	..	2	..	2	..	..	++	—	1	+++	..	—
18	F	10	..	3	7	6	4	..	++	+	2	+++	..	+
19	F	11	..	4	7	7	4	..	+++	+	4	++	..	+
20	M	10	..	4	6	10	..	..	+++	—	..	+	..	+
21	F	19	4	6	9	15	4	..	+++	++	..	+++	+	+

2. Spasticity and narrowness of the loops of greater or less degree (17 cases). Sometimes, during observation, in a place where no capillary existed, it was possible to note the forward movement of the erythrocytes, either in an interrupted way or with a great speed, marking the pattern of a loop. Sometimes, with the flowing of the erythrocytes toward the vein, the area was left empty, and some of the capillaries were disappearing. In some cases the spasm was of such a degree that the capillary loops seemed divided by the row of erythrocytes into two or more fragments. Fragmentation was present in half the cases.

3. Thickening of the intermediate portion of the loop, or button-like nodule on the top. This change was absent in five cases only and was present in the remaining 16 cases. Whether this thickening, which also was observed by Chiavacci and Putnam [12] in 32 of their 48 cases, is an indication of a thrombus in the loop is an open question. The present study has been concentrated particularly on this point.

TABLE 2.—*Similar Abnormalities in Capillary Pattern in Cases of Other Neuropsychiatric Disorders and in Normal Controls*

No. of Cases			Abnormalities in Capillary Pattern of Group B																			
				Length			Thickness			Spasticity				Thickening of Intermediate Portion	Tortuosity				Venous Plexus	Circulation	
A*	B†	Diseases	No. of Capillaries	Long	Normal	Short	Thin	Normal	Thick	+	++	+++	Fragmentation		+	++	+++	++++		Present	Absent
24	10	Brain tumor	150	26	98	26	60	80	10	4	3	2	44	51	7	1	2	..	..	7	3
27	10	Hemiplegia	93	4	25	64	71	15	7	2	3	3	11	11	6	2	1	1	1	8	2
29	7	Polyneuritis	80	4	27	49	54	26	..	3	1	1	39	37	4	2	1	..	..	7	..
39	6	Epilepsy	107	5	61	41	59	48	..	2	1	2	10	30	2	2	1	1	..	5	1
5	5	Amyotrophic lateral sclerosis	36	..	20	16	20	15	1	1	2	2	16	18	3	2	..	..	2	4	1
7	4	Parkinson's syndrome	40	..	17	23	36	4	..	..	2	2	10	10	1	1	2	..	..	3	1
23	4	Migraine	30	..	14	16	17	13	..	1	2	..	8	8	2	2	..	..	..	3	1
5	3	Poliomyelitis	33	..	17	16	16	17	..	2	1	..	10	19	2	1	..	..	..	2	1
4	3	Choreoathetosis	37	..	17	20	20	17	..	2	1	..	7	7	2	1	..	..	..	2	1
2	2	Facial hemiatrophy	24	..	7	17	19	5	..	..	..	2	5	7	1	1	..	..	..	1	1
2	2	Combined sclerosis	17	..	17	..	10	7	..	..	2	..	..	7	2	..	..	..	..	1	1
11	2	Cerebrospinal syphilis	20	..	20	..	13	7	..	1	1	..	2	12	2	..	..	..	..	2	..
29	4	Arteriosclerosis	40	4	24	12	22	18	..	1	1	1	15	4	1	2	1	..	1	4	..
12	5	Toxicomania (alcoholism)	65	6	41	18	50	15	..	1	2	2	29	13	2	2	..	1	1	5	..
43	2	Dementia praecox	22	3	15	5	14	6	2	..	1	1	8	7	..	..	2	..	..	2	..
48	4	Oligophrenia	21	2	17	2	10	10	1	1	..	..	5	5	2	1	1	..	1	2	2
45	7	Psychoneurosis	74	15	29	30	37	34	3	1	3	3	28	7	5	1	1	..	4	7	..
30	3	Miscellaneous	27	..	7	20	20	7	..	..	3	..	7	10	..	2	..	1	1	1	2
50	5	Normal controls	50	4	30	16	22	28	..	2	2	1	5	7	4	..	1	..	..	4	1

* Column A shows the number of patients examined.
† Column B shows the number of cases in which there were abnormalities similar to those seen in multiple sclerosis.

If the finger, with thickening of the intermediate portion of its capillary, is pressed and released at different points and the capillaries are stimulated by a pin, jerkiness, discontinuation, and slowing of the circulation will be observed, and an opposite flow, from the vein toward the artery, may be noted. Thus, it is possible to empty and to fill the capillaries again. The presence of circulation in a capillary with thickened intermediate portion, its disappearance on pressure, and recovery of its previous shape on release of pressure may be good proof that there is no thrombus. In order to speak more definitely on this point, in collaboration with Güldoğan, a pathologist, I made autopsy observations in six cases, having serial cross and horizontal sections on the same nail beds, but noticed no formation resembling a thrombus.

4. Circulation. It was not possible to observe the circulation in four cases. In the remaining 17 cases the circulation was irregular; it did not have the same speed in each capillary. In some it was slow, and in others, rapid or jerky.

The proportion of abnormalities in shape and circulation of the capillaries of the type seen in multiple sclerosis is presented in cases of other neuropsychiatric diseases and in a number of normal persons, as recorded in Table 2.

SUMMARY

Capillaroscopic observations on 21 patients with an established diagnosis of multiple sclerosis were made, with the purpose of comparison with the characteristics of the capillaries of 50 normal persons and of 380 patients with various neuropsychiatric conditions. The following results were obtained.

The circulation was faulty—slow, interrupted, and irregular, and the capillaries were thin, small, spastic, and fragmented. These observations point to the vascular disorder in multiple sclerosis.

Thickening of the intermediate portion of the loops or button-like nodules at the top were common enlargements, and some capillaries showed superposition or kinking of the two stems of the loops. These capillary changes were not characteristic of a thrombus.

These changes should not be considered real evidence of multiple sclerosis, for the same capillary forms have been observed in other neuropsychiatric diseases.

It is very probable that a spasm has an important part in the pathogenesis of the disease.

30 Yüksel Cd.

News and Comment

AMERICAN PSYCHOSOMATIC SOCIETY'S NINTH ANNUAL MEETING

The American Psychosomatic Society will hold its ninth annual meeting at the Drake Hotel, Chicago, on Saturday and Sunday, March 29 and 30, 1952.

The program committee would like to receive titles and abstracts of papers for consideration for the program by Dec. 1, 1951. The time allotted for the reading of each paper will be 20 min. The committee is interested in investigations in the theory and practice of psychosomatic medicine as applied to adults and children in all the medical specialties and in contributions in psychophysiology and ecology. Papers accepted for presentation at the meeting will be submitted to the editorial Board of *Psychosomatic Medicine* for possible publication in that journal.

Material for consideration by the program committee should be sent, in duplicate, to Dr. Roy R. Grinker, chairman, 714 Madison Ave., New York 21.

DR. BRACELAND ASSUMES POST AT INSTITUTE OF LIVING

Dr. Francis James Braceland, formerly consultant in psychiatry at the Mayo Clinic, Rochester, Minn., has taken over his new duties as Psychiatrist-in-Chief at the Institute of Living, Hartford, Conn. Dr. Braceland is secretary and treasurer of the American Board of Psychiatry and Neurology and a member of the executive committee of the Council of the American Psychiatric Association. At the Institute of Living, he succeeds to the post occupied for 19 yr. by Dr. C. Charles Burlingame, who died in July, 1950. The Institute is the third oldest psychiatric hospital in the United States, and one of the country's largest private psychiatric hospitals.

DR. MASSERMAN APPOINTED CONSULTANT TO SECRETARIAT OF UNITED NATIONS

Dr. Jules H. Masserman, Associate Professor of Nervous and Mental Diseases at Northwestern University Medical School, and Scientific Director, National Foundation for Psychiatric Research, has been appointed Consultant to the Secretariat of the United Nations and designated by the World Health Organization to present a series of lectures at various universities throughout Europe, including Scandinavia, in October and November of this year. During his stay in England Dr. Masserman will also address the British Royal Society on his research studies and their significance to dynamic concepts of personal and social behavior.

Abstracts from Current Literature

EDITED BY DR. BERNARD J. ALPERS

Anatomy and Embryology

INVASION OF THE EPIDERMIS OF THE REGENERATING FORELIMB OF THE URODELE, TRITURUS, BY NERVE FIBERS. MARCUS SINGER, J. Exper. Zool. **111**:189 (July) 1949.

The stumps of forelimb regenerates of the adult Triturus were removed at intervals from five to 38 days after amputation and prepared for histological examination (silver-proteinate and orange-G stains). Nerve fibers were found to penetrate the epidermis of the regenerate in greater numbers than in the normal skin. This invasion occurs within a few days after amputation, and the fibers reach a maximum number within the first 10 to 20 days. They decrease in number thereafter and appear only occasionally after 35 days. More fibers are seen distally in the epidermis than proximally. The fibers may enter the epidermis singly or in fascicles. The fibers appear to be entirely intercellular, winding among the cells to reach the outer cuticular layers or growing for great distances tangentially. These nerve fibers are unaccompanied by Schwann cells or a myelin sheath. Physiological studies show that the regenerate is much more sensitive than the normal limb, on observation supporting the histological observations. This previously unreported observation on nerve fibers in the epidermis of the regenerate suggests a relation between nerve and epidermis important for the regenerative process.

REID, New Bunswick, N. J.

EXPERIMENTS ON PARTIALLY DENEUROTIZED NERVES: I. ABSENCE OF BRANCHING OF RESIDUAL FIBERS. M. V. EDDS JR., J. Exper. Zool. **111**:211 (July) 1949.

Partial deneurotization of the sciatic, pudendal, or long thoracic nerves in adult white rats was brought about by surgical elimination of contributory branches of the spinal nerves, fourth lumbar, sixth lumbar, or sixth cervical, respectively. The ends of the cut spinal nerves were capped with methyl methacrylate in acetone. After postoperative intervals of nine to 366 days the deneurotized nerves were studied and compared with their contralateral controls.

There was a proportionate and permanent reduction in the number of myelinated axons in the sectioned nerves. Only when regenerating fibers of the interrupted spinal nerves escape into such nerves, or when the intact, contributory spinal nerves are accidentally damaged is there an increase in the fiber number.

Edds concludes that these results eliminate intraneural fiber branching as a factor in the spontaneous recovery of partially denervated muscles and that they reemphasize the importance of intramuscular sprouting of the residual axons.

REID, New Bunswick, N. J.

PROLIFERATION, DIFFERENTIATION AND DEGENERATION ON THE SPINAL GANGLIA OF THE CHICK EMBRYO UNDER NORMAL AND EXPERIMENTAL CONDITIONS. V. HAMBURGER and R. LEVI-MONTALCINI. J. Exper. Zool. **111**:457 (Aug.) 1949.

Observations on the normal development of the spinal ganglia were made on a series of chick embryos from two and a half days of incubation until the time of hatching. Two groups of neurons, differing in rate and mode of differentiation and in size, can be distinguished. Indirect evidence indicates that the early and rapidly differentiating neurons are exteroceptive, while the neurons that differentiate belatedly include the proprioceptive neurons. Toward the end of incubation both morphological and size differences disappear.

Mitotic activity in the spinal ganglia reaches its peak at the fifth and sixth day of incubation, and is almost terminated at the ninth day. The number of mitoses is higher in the ganglia innervating the limbs (brachial and lumbosacral) than in the cervical and thoracic ganglia.

A large-scale degeneration of early differentiated neuroblasts was discovered in the cervical and thoracic ganglia. The presence of macrophages during this period was established by appropriate staining methods. There is no such degeneration in the ganglia innervating the limbs. The differences in size between the ganglia innervating the limbs and adjacent ganglia result partly from differences in mitotic activity and partly from selective degeneration.

Observations were also made on ganglia affected by limb extirpation or by limb transplantation. Mitotic activity is reduced by limb extirpation and is increased by peripheral overloading by about 20% in either direction. The increase in number of early differentiating neurons in overloaded ganglia may amount to 80%. Hence, peripheral factors appear to control the differentiation process of indifferent cells.

Limb extirpation results in rapid degeneration and disappearance of numerous early differentiating neurons in the limb ganglia (after five to six days of incubation), a process which is comparable in all details to that occurring in normal cervical and thoracic ganglia. There is atrophy of late-differentiating neurons.

Discussion of the complex and heterogenous nature of the phenomena covered by the terms "hypoplasia" and "hyperplasia" leads to the suggestion that a distinction be made between "numerical" and "volumetric" hypoplasia or hyperplasia.

Two basically different mechanisms operate in the control of development of spinal ganglia by peripheral factors: (1) The periphery controls the proliferation and initial differentiation of undifferentiated cells, which have no connection of their own with the periphery; (2) the periphery provides the conditions necessary for continued growth and maintenance of neurons in stages following the first outgrowth of neurites.

REID, New Brunswick, N. J.

EXPERIMENTS ON PARTIALLY DENEUROTIZED NERVES: II. HYPERTROPHY OF RESIDUAL FIBERS. M. V. EDDS JR., J. Exper. Zool. **112**:29 (Oct.) 1949.

In order to test the effect on nerve-fiber size of increasing the peripheral connections, the long thoracic nerves of the rat were partially deneurotized by cutting the fibers of the sixth cervical nerve root. The size of the experimentally overloaded nerves (seventh and eighth cervical) was then compared with that of the contralateral (normal) fibers.

Five to 30 wk. after operation the fiber-size spectrums showed a small shift of the fibers of the experimental nerves into classes of larger size, a mean increase in diameter of 0.56 μ (approximately 10%), which is a statistically significant difference ($P = 0.001$).

Each experimental fiber population, like its control, has a bimodal distribution of sizes. These two subpopulations may be divided arbitrarily for separate analysis. In the experimental nerves the mean diameter of the small-size group is 0.42 μ, that is, 15% greater than that of the control fibers ($P = 0.002$). In the large-size fiber groups, the test fibers exceed their controls by 0.85 μ, or 9.9% ($P = 0.01$).

Significant differences between experimental and control cumulative-percentage curves show that the test nerves have fewer nerves below any given size, and more above it, than do their controls. These differences suggest that a certain number of the fibers in each original size-class has hypertrophied enough to shift into the next higher class. Fibers below 4 μ have hypertrophied less than the larger fibers. Most fibers seem to have moved up only one size-class, but it is possible that some excessively overloaded fibers have shifted several classes.

These results offer further evidence that peripheral tissues exert a direct influence on the nerve cells which supply them.

REID, New Brunswick, N. J.

EFFECTS OF DELAYED DENERVATION ON REGENERATIVE ACTIVITY IN LIMBS OF URODELE LARVAE. E. G. BUTLER and O. E. SCHOTTÉ, J. Exper. Zool. **112**:361 (Dec.) 1949.

Amputated limbs of the larvae of either Amblystoma punctatum or Amblystoma opacum (larvae 20 to 50 mm. in length) were allowed to regenerate from two to 14 days before they were denervated. Histological studies were then made to determine the effects of the lack of nerves on limb regeneration. Constant temperature conditions were maintained in all experiments.

Denervation in the first five days after amputation (preblastema stage) results in changes which are exactly like those which occur when denervation is concomitant with amputation. When the denervation is continued, all the tissues at the distal end undergo dedifferentiation, and regression of the limb follows.

After denervation in young blastema stages (six, seven, and eight days after amputation) one of three types of change may occur: rapid decrease and disappearance of the blastema, continu-

ation of the blastema in an inactive state, or prolonged inactivity, followed by regression of the blastema. However, in all cases there are eventual regression and destruction of the limb structures.

From the seventh to the ninth day the blastema is in a "critical period" of becoming emancipated from neural influence, for begining on or about the 10th day after amputation removal of the nerves has no influence on the normal rate of regeneration. Growth may be slightly retarded.

From the results of this study, Butler and Schotté conclude that neural influence is essential for the early mobilization of the cells which form the blastema and for the intiation of morphogenetic activities within the blastema, but that neural influence is not essential for the growth, morphogenesis, and histogenesis of the regenerate.

REID, New Bunswick, N. J.

THE EFFECTS OF NOTOCHORDECTOMY IN AMBLYSTOMA MEXICANUM. I. C. KITCHIN, J. Exper. Zool. **112**:393 (Dec.) 1949.

The notochord was removed through a ventral incision from embryos of Amblystoma mexicanum at a stage just following the appearance of the fully formed neural plate.

After notochordectomy there was complete failure of the pronounced anteroposterior stretching of the embryo which usually characterizes development after the embryonic tail-bud stages. Kitchin concludes that a fundamental function of the notochord is the stretching of the embryonic axis, due to the accelerated growth and expansion of the notochord, which exactly coincides with the active stretching period of the embryo.

Shifting of the lateral-myotome tissues to fill the space left vacant by the notochord caused the formation of common medial myotomes. This abnormal fusion of myotome did not affect the gross structure of the neural tube and the distribution of the gray and white matter which developed in the cord. Comparison of this result with those in previous experiments in which myotome fusion just prior to differentiation of the neural plate led to extreme modification of the neural-tube structure permits the author to conclude that the structure of the neural tube is determined during, and as a part of, the initial induction of the neural plate.

In the notochordectomized animals the ganglia maintained their normal position in relation to the lateral surfaces of the normal neural tube.

The axial cartilages of the trunk developed as a single fused mass of cartilage, attached anteriorly to the posterior edges of the cranial cartilages and extending only to the middle of the trunk. There was no indication of metameric segmentation or any tendency to assume the form of normal arches. The peculiar distribution of cartilage may be explained by assuming that the notochord normally acts to induce and localize cartilage formation at the individual sclerotome levels. In the absence of the notochord, the inductive capacity of the cartilage itself is responsible for producing abnormal and massive cartilage deposits. Kitchin suggests that in normal development a combination of notochordal contact and the configuration of the adjacent structures is responsible for the initial form assumed by the axial cartilages.

REID, New Brunswick, N. J.

NATURE OF THE GOLGI APPARATUS: I. PARALLELISM BETWEEN INTERCELLULAR MYELIN FIGURES AND GOLGI APPARATUS IN SOMATIC CELLS. G. E. PALADE and A. CUDE, J. Morphol. **85**:35 (July) 1949.

Intracellular myelin figures were produced exerimentally in homogenates of a variety of vertebrate somatic cells, including glandular epitheliums from liver, kidney, pancreas, and chicken gizzard, epitheliums from intestine and epididymis, nerve-cell perikarya, fibrocytes, and smooth-muscle fibers. The addition of 40 to 55% ethyl alcohol to the medium produced myelin figures, developed at the expense of the lipid inclusions, which had existed as refringent droplets in the fresh cells. These cell inclusions stain with Sudan black B, showing their lipid nature, and are able to concentrate neutral red and form myelin figures, indicating their appreciable content of phospholipid.

The intracellular myelin figures induced by ethyl alcohol duplicate in morphological and topographical features the Golgi apparatus of corresponding cells. The results suggest that the Golgi apparatus is a myelin figure, or a complex of myelin figures, artificially induced in cells during the preparation of the cytological specimens.

REID, New Bunswick, N. J.

CORRELATED STUDIES OF SENSE ORGANS AND NERVES OF THE LATERAL-LINE IN LIVING FROG TADPOLES: III. EXPERIMENTS ON THE ORANGE GRANULES AND SENSE HAIRS OF DENERVATED AND INNERVATED ORGANS. C. C. SPEIDEL, J. Morphol. **85**:113 (July) 1949.

Experiments have been carried out to determine to what extent the two specialized structures (orange granules and sense hairs) of the sense cells of the lateral-line organs of frog tadpoles (Rana clamitans) are influenced by the presence or absence of the specific nerve supply.

In both denervated and innervated organs, the orange granules disappear when the tadpoles are transferred from their natural pond habitat to an aquarium and reappear when the animals are returned to the pond.

Sense hairs vary in number and length in individual organs. Injured sense hairs develop a characteristic bleb at the tip, but recover quickly by losing the bleb and forming a new pointed tip. Denervation does not alter any of these sense-hair reactions.

Speidel concludes that both orange granules and sense hairs are relatively independent of nerve influence as regards their first formation, their growth, and their regeneration. However, they are subject to the general long-range trophic influence which the lateral-line nerves exert over the lateral-line organs.

Histories of orange granules and of sense hairs have been recorded by kinetography.

REID, New Bunswick, N. J.

HISTOLOGICAL EFFECTS ON THE EMBRYO FOLLOWING X-IRRADIATION. ROBERTS RUGH, J. Morphol. **85**:283 (Nov.) 1949.

Larvae of Amblystoma punctatum (2.2 cm. total length) were given a single dose of 15,000 r of x-rays and were allowed to live one week before they were killed and prepared for study of the histological and cytological changes.

The tissues most resistant to x-ray damage were cartilage and muscle. There was no evidence of damage to the matrix of the cartilage or to the myoplasm or myofibrillae of the muscle.

The central-nervous tissue and its related sense organs were most sensitive to x-ray damage. Neuroblasts were sloughed off into the brain cavity, and cells and nuclei were in all stages of degeneration. There was no evidence of growth. This tissue was the most actively differentiating type at the time of irradiation.

The larval or embryonic tissues are variously sensitive to x-ray damage, but in a manner quite different from the adult tissues.

The discussion considers the possibility that the so-called resting (premitotic or postmitotic) cell is more severely damaged than the more obvious mitotic phases, since there was complete inhibition of mitoses in all nonmitotic cells.

REID, New Bunswick, N. J.

Physiology and Biochemistry

ABNORMALITIES OF WATER AND ELECTROLYTE METABOLISM IN RATS WITH HYPOTHALAMIC LESIONS. J. A. F. STEVENSON, L. G. WELT, and J. ORLOFF, Am. J. Physiol. **161**:35 (April) 1950.

In rats, after bilateral lesions of the ventromedian region of the hypothalamus, the mean concentration of serum sodium is significantly higher than in intact controls when food and water are freely available. A similar situation exists when both the hypothalamic and the control animals have been deprived of food and water for 16 hr. When food alone is removed for 16 hr., the difference in concentration of serum sodium between the experimental and the control animals was not found to be significant in the number studied.

Animals with lesions in the ventromedian region of the hypothalamus usually exhibit hyperphagia and obesity and chronic disturbances of water metabolism. The observations of Stevenson and his co-workers support the hypothesis that the delayed excretion of water loads and the increased renal-tubule reabsorption shown by these animals are reflections of a chronic state of relative dehydration. The lower ratios for water-food intake imply a deficit in the neural mechanism responsible for thirst and its alleviation.

ALPERS, Philadelphia.

RECRUITMENT PHENOMENON IN CRANIOCEREBRAL TRAUMA: REPORT OF REPRESENTATIVE CASES. M. SALTMAN, Arch. Otolaryng. **52**:782 (Nov.) 1950.

The theory of loudness recruitment has been formulated by Fowler. Clinically, this phenomenon is utilized to distinguish a conduction impairment and a nerve defect. In the words of Fowler, "The recruitment of loudness with intensity enables one to diagnose obstruction from nerve deafness." By means of the loudness-balance test, it has become possible to make a quantitative determination of the degree of recoupment.

The author reports a case of head injury without fracture of the skull, a case of linear fracture of the skull with bleeding ear, and a case of fracture of the skull with injury to the brain stem. In all cases hearing was involved. In these cases of craniocerebral trauma, the recruitment phenomenon was absent. It is possible that the pathologic changes consist of contusion of the brain with petechial hemorrhages involving the cochlear nuclei. In the third case the vestibular pathways were also involved.

ALPERS, Philadelphia.

TREMOR AND CHANGES IN REFLEX STATUS PRODUCED BY DDT IN DECEREBRATE, DECEREBRATE-DECEREBELLATE AND SPINAL ANIMALS. R. B. BROMILEY and P. BARD, Bull. Johns Hopkins Hosp. **84**:414 (May) 1949.

Bromiley and Bard report that others have studied the effect of DDT (2,2-bis[*p*-chlorophenyl]-1,1,1-trichloroethane) on the intact mammal and have observed the presence of abnormal muscle tremors, dysmetria, and hypermetria during walking; exaggerated standing, and often inability to arrest forward progression. In both acute and chronic poisoning tonic and clonic convulsions may occur. Several other investigators have suggested that in DDT intoxication the cerebellum is selectively affected.

The authors describe in detail the methods employed for the investigation of the effect of DDT on cats and dogs. In some instances the animals were studied several weeks or months after surgical exclusion of one or another part of the central nervous system or after transection of the spinal cord. In other instances animals which were recently operated on were subjected to the administration of DDT.

Bromiley and Bard state in their summary and conclusions that in acutely decerebrate cats DDT produces a tremor which is indistinguishable from that induced in normal animals by the poison. It also causes signs of an altered central state or "set of the center," which is indicated by a tendency of the forepaws to be flexed with claws protruded, crossed (bilateral) knee jerks, appearance of the "ipsilateral head-tail response," and some increase in reflex excitability, especially of extensor responses.

The effects produced by DDT in the decerebrate cat are not essentially modified by removal of the cerebellum. In the decerebrate-decerebellate cat DDT may evoke a tonic-clonic convulsion. A seizure of this type was seen in a dog which was given DDT 23 mo. after total uncomplicated ablation of the cerebellum.

While these experiments demonstrate that forebrain, mesencephalon, and cerebellum are in no way necessary for the development of the tremor characteristic of the intact animal poisoned by DDT, they do not permit any conclusion as to the site or sites of the action of this substance which results in abnormalities of stance and locomotion in the animal with central nervous system intact.

DDT produces tremor in muscles innervated from segments of the spinal cord which have been deprived of all neural connections with the brain. This fact has been shown in animals with cord transected at a thoracic level and studied either in the chronic spinal state or in the acute decerebrate condition. When such animals are given DDT, the tremor usually appears in the fore parts. When the intoxication is light, as judged by the behavior of the fore parts, the tremor may appear only reflexly in the hind parts in response to a mechanical disturbance of that portion of the body. With deeper levels of poisoning, tremor occurs spontaneously in the hind parts but may not attain the vigor of the activity present in muscles innervated from above the transection. Sometimes, but by no means invariably, the tremor in the muscles innervated from the isolated cord is not as fine as that in the fore parts, the coarse component being more prominent.

DDT acts to alter the reflex activities of the isolated lumbosacral portion of the cord. In the case of the cat there are augmentation of flexor tone, lowering of threshold of the flexion reflex, and irradiation of impulses from proprioceptors of the knee extensors to give a crossed knee jerk. In the spinal dog the reflexes involving extensor muscles of the hindleg become more active and show very long after-discharges.

GUTTMAN, Wilkes-Barre, Pa.

THE PROBLEM OF SPASM IN SKELETAL MUSCLE: A CLINICAL AND LABORATORY STUDY. A. HARELL, S. MEAD, and E. MUELLER, J. A. M. A. **143**:640 (June 17) 1950.

This study was undertaken in an attempt (1) to investigate the meaning of the spasm concept and to formulate a definition sufficiently inclusive and generally acceptable, (2) to discover simple means by which to demonstrate this condition objectively, and (3) to determine whether there is by necessity a definite mutual cause-and-effect relationship between pain and spasm.

The authors define spasm in skeletal muscle as a reversible state of sustained involuntary contraction accompanied with muscular shortening and associated with electrical-potential change.

Groups of patients with various types of low-back pain, fractures, and poliomyelitis were examined carefully for the existence of muscular spasm, using electromyographic techniques. Only in an inconsequentially small number could such spasm be detected. They believe that the clinical diagnosis of spasm in peripheral conditions, such as backache, fracture, or poliomyelitis, will be erroneous in a large percentage of cases.

Clinical and experimental work is described which shows that there seems to be no specific cause-and-effect relationship between spasm nd painful peripheral state.

Harell and his co-workers make a strong plea for thoughtful use of the term spasm, differentiating it carefully from spasms, spasticity, tonus, contracture, cramp, and rigidity.

ALPERS, Philadelphia.

CARBONIC ANHYDRASE IN THE BRAIN OF THE NEWBORN IN RELATION TO FUNCTIONAL MATURITY. W. ASHBY and E. M. SCHUSTER, J. Biol. Chem. **184**:109, 1950.

From studies of the carbonic anhydrase content of the central nervous system of fetal cattle and of premature human infants, it was previously reported that this enzyme first appeared in greater amounts in the lower centers and that the maximum amount progresses to higher centers as the fetus develops. The enzyme was not found in the cerebrum of fetal cattle until the last month of gestation, during which it rapidly rose to an amount equal to half that of the adult animal. Although a similar progressive increase in the enzyme was shown in the human fetus, as studied in premature births, none was found in the cerebrum at 8-months' gestation or in the cerebrum of an 8-lb. (3,628-gm.), full-term infant. Although this child was well developed, the cause of death was not evident. The normality of this finding for the central nervous system was therefore questioned. There is a late appearance of carbonic anhydrase in the cerebrum of the young of the dog, the cat, the rat, and the rabbit, animals born in an immature condition; this is in contrast to its presence at birth in the cerebrum of animals which are more mature when born, such as the calf and the guinea pig. The data suggest correlation between the appearance of the enzyme in the cerebrum and the beginning of cerebral functioning, as indicated by the parallel maturation of certain sense organs and the first appearance of alpha brain waves, as reported in the literature. The fact that there is an even later appearance of the enzyme in the central nervous system of the rat, dog, rabbit, and cat than in that of the human infant increases the probability that the absence, previously reported, of carbonic anhydrase in the cerebrum of the human newborn infant may be normal.

PAGE, Cleveland.

PORPHYRIN FORMATION IN HEMOGLOBIN METABOLISM IN CONGENITAL PORPHYRIA. I. M. LONDON, R. WEST, D. SHEMIN and D. RITTENBERG, J. Biol. Chem. **184**:365, 1950.

The studies reported here were conducted on a patient with congenital porphyria who excretes large amounts of uroporphyrin I and coproporphyrin I. They were directed to the following problems: (*a*) to determine whether glycine (amino-acetic acid) is specifically utilized in the biologic synthesis of porphyrins related to the etioporphyrin-I configuration as it is utilized in the synthesis of protoporphyrin, which is related to the etioporphyrin-III configuration; (*b*)

to measure the rates of formation (and degradation) of uroporphyrin I and coproporphyrin I; (*c*) to investigate the life span and pattern of destruction of the erythrocyte and the origins of bile pigment in this disease. Glycine is specifically utilized in the biologic synthesis of porphyrins related to the etioporphyrin-I configuration. The rates of formation and degradation of uroporphyrin I and of coproporphyrin I in a subject with congenital porphyria are found to be rapid. A normal average life span of the erythrocyte of about 120 days was observed in this subject with congenital porphyria. A large part, at least 31%, of the stercobilin in this subject is derived from sources other than the hemoglobin of mature, circulating erythrocytes. The nature of these possible sources is discussed.

PAGE, Cleveland.

INVESTIGATION OF THE AMINOACIDURIA IN WILSON'S DISEASE (HEPATOLENTICULAR DEGENERATION): DEMONSTRATION OF A DEFECT IN RENAL FUNCTION. A. M. COOPER, R. D. ECKHARDT, W. W. FALCON, and C. S. DAVIDSON, J. Clin. Invest. **29**:265 (March) 1950.

The experiments here described by Cooper and his co-workers were undertaken to elucidate the mechanism of the excessive loss of amino acids in Wilson's disease (hepatolenticular degeneration) with respect to the site and type of disorder.

Studies on six patients with Wilson's disease yielded the following results:

The average daily excretion of alpha-amino-nitrogen in the urine was consistently elevated. The excretion of alpha-amino-nitrogen during feeding *ad libitum* could be accounted for by the fasting rate of excretion, which averaged three times the normal. The rapid infusion of amino acids did not result in a significantly greater loss of amino acids in the patients than in the normal subjects.

Although the plasma-amino-nitrogen concentration of the patients averaged slightly above the normal, this did not explain their amino-aciduria. There was no demonstrable defect of intermediary amino-acid metabolism.

The occurrence in patients with Wilson's disease of an excessive amino-acid excretion in the fasting state would indicate a lowered renal threshold for amino acids. However, a greater than normal loss of amino acids following the ingestion of protein foods or the injection of protein hydrolysates was not observed. Renal glycosuria was demonstrated in three patients. Another patient presented evidence of deranged calcium and phosphorus metabolism and osteomalacia.

The authors believe the kidney to be the site of the defect resulting in excessive loss of amino acids, but the type of abnormality is not explained.

ALPERS, Philadelphia.

EFFECTS OF DIHYDROERGOCORNINE ON THE CEREBRAL CIRCULATION OF PATIENTS WITH ESSENTIAL HYPERTENSION. J. H. HAFKENSCHIEL, C. W. CRUMPTON, J. H. MOYER and W. A. JEFFERS, J. Clin. Invest. **29**:408 (April) 1950.

It has previously been reported by Hafkenschiel and his co-workers that normotensive patients to whom dihydroergocornine was given had insignificant decreases in cerebral blood flow, cerebral vascular resistance, and oxygen uptake. However, the mean arterial pressure was significantly decreased. The present report is concerned with the effect of dihydroergocornine on mean arterial pressure, cerebral blood flow, cerebral oxygen uptake, and cerebral vascular resistance in 12 patients with essential hypertension.

The authors found that cerebral blood flow, cerebral arteriovenous oxygen difference, and cerebral oxygen metabolism were unchanged when the mean arterial blood pressure was significantly decreased.

They conclude that dihydroergocornine appears to have produced a significant decrease in the cerebral vascular resistance, allowing for cerebral metabolic homeostasis.

ALPERS, Philadelphia.

A NEUROLOGICAL EVALUATION OF THE CUTANEOUS HISTAMINE REACTION. I. S. COOPER, J. Clin. Invest. **29**:465 (April) 1950.

Lewis and Grant described the triple response of cutaneous vessels to injury: This response consists of an initial red reaction, spreading flare, and localized wheal. The present study deals with the neurologic basis for the spreading flare.

Paired intradermal injections of 0.1 cc. of histamine in 1 : 5,000 and 1 : 10,000 aqueous dilutions were made into anesthetic and normally sensitive cutaneous areas of 50 young men who presented lesions at various levels of the nervous system. The diameter of the initial red reaction was measured 30 sec. after injection, and the diameters of the spreading flare and wheal five minutes after injection. Whenever the reaction in an anesthetic area differed from that in its control site, a "stroke" reaction was produced, and similar measurements were made.

Cooper found that the spreading-flare phase of the triple response is absent after complete transection of a spinal nerve. The spreading flare is absent or greatly decreased in dermatomes below the level of complete transection of the spinal cord and after isolation of the spinal cord from nerve centers cephalad to the pons. Neither preganglionic sympathetic pathways nor the final common pathways are essential to the spreading flare.

Cooper suggests that the axon reflex alone cannot subserve the neurogenic mechanism of the spreading flare, and this mechanism may include a suprasegmental reflex arc, the afferent arm of which reaches as high as the diencephalon, or higher. The afferent and efferent impulses in this reflex travel via the dorsal nerve roots.

ALPERS, Philadelphia.

ROLE OF THE VESTIBULAR APPARATUS IN THE PRODUCTION OF NAUSEA AND VOMITING FOLLOWING THE ADMINISTRATION OF MORPHINE TO MAN. A. RUBIN and J. WINSTON, J. Clin. Invest. **29**:1261 (Oct.) 1950.

Morphine has among its disturbing side effects the production of nausea and emesis. Studies have suggested that morphine may disturb vestibular function and that the vestibular activity incident to ambulation may then result in an increase in nausea and emesis. To investigate this possibility, the authors examined the responses to vestibular stimulation in 20 healthy adults before and after the administration of morphine.

It was found that morphine sulfate produced a significant decrease in vestibular response. Vestibular stimulation following the administration of morphine sulfate resulted in a notable increase in nausea and emesis. Amphetamine sulfate was of no apparent benefit in relieving this emesis. Dimenhydrinate, given either orally or rectally, appeared to prevent and relieve nausea, vomiting, and vertigo following morphine, dihydromorphinone (dilaudid®) and meperidine, and its use therapeutically and prophylactically with these drugs is suggested.

Neither dimenhydrinate nor amphetamine altered the vestibular changes produced by morphine. Vestibular changes following morphine resulted in no significant changes in blood pressure or pulse rate.

ALPERS, Philadelphia.

CEREBRAL BLOOD FLOW AND OXYGEN CONSUMPTION IN NEUROSYPHILIS. J. L. PATTERSON JR., A. HEYMAN, and F. T. NICHOLS JR., J. Clin. Invest. **29**:1327 (Oct.) 1950.

The blood vessels of the brain are involved to a major extent in the pathologic changes of late neurosyphilis. Narrowing or obliteration of the vascular lumen frequently results.

The recent development by Kety and Schmidt of the nitrous-oxide method for the determination of cerebral blood flow has provided a reasonably accurate technique for the study of the cerebral circulation and metabolism. Using this technique, Patterson and his associates determined the cerebral blood flow, oxygen consumption, and vascular resistance in 58 patients with neurosyphilis and in 16 control subjects.

It was found that in patients with dementia paralytica and meningovascular syphilis the mean cerebral blood flow and cerebral oxygen consumption were significantly reduced, whereas the mean vascular resistance of the brain was significantly increased. In patients with asymptomatic neurosyphilis these functions were within normal range. In patients with dementia paralytica, a definite correlation was found between the degree of mental deterioration and the reduction in cerebral oxygen consumption.

In patients with meningovascular syphilis treatment was usually followed by a rise in cerebral blood flow, while the cerebral oxygen consumption showed a variable response. Treatment with penicillin and fever was followed by a rise in the cerebral oxygen consumption in those patients with dementia paralytica who had low pretreatment values. This increase in cerebral oxygen consumption was accompanied with improvement in mental state.

ALPERS, Philadelphia.

CAPILLARY RESISTANCE STUDIES IN MULTIPLE SCLEROSIS. M. H. SHULMAN, L. ALEXANDER, O. F. EHRENTHEIL, and R. GROSS, J. Neuropath. & Exper. Neurol. **9**:420 (Oct.) 1950.

This study was undertaken to determine whether or not the status of the capillary system could be used as an index of the degree of the involvement in multiple sclerosis. Fifty patients with proved multiple sclerosis were tested at two- to four-week intervals over a period of eight months. In order that differences in individual readings should be avoided, a single examiner was chosen to reexamine the entire group, using definite and prescribed criteria. The same examiner then tested a statistically comparable group of normal subjects. All the findings were then subjected to statistical analysis.

As groups, manual laborers showed the highest capillary resistance; sedentary normal subjects, intermediate values, and patients with multiple sclerosis, the lowest. That patients with multiple sclerosis gave the lowest reading because of inactivity was disproved by the finding that patients in remission, although as active as most normal persons, showed no higher readings than the other groups of patients with the disease.

While normal subjects showed no association between capillary resistance and age, multiple-sclerosis patients did show some indication of a decline in resistance with the duration of the disease.

Differences in capillary resistance among groups of multiple-sclerosis patients in various stages of disease were not of sufficient significance, mainly because of the overlap among these groups and the limited precision of the capillary-resistance tests, to indicate the usefulness of this test at present for the evaluation of the severity of the disease and the prognosis for individual patients.

ALPERS, Philadelphia.

LACK OF REGENERATION IN SPINAL CORD OF RAT. J. W. BARNARD and W. CARPENTER, J. Neurophysiol. **13**:223 (May) 1950.

Barnard and Carpenter cut across the spinal cords of 159 rats in the midthoracic region. The ends of the cords were completely visualized to ensure complete transection. Both autotransplants and homotransplants of fresh sciatic nerve, degenerated sciatic nerve, and muscle were placed in the gap between the cord ends in various groups of animals. A tantalum cuff or cylinder was inserted over the cut cord ends in another group. The animals were kept alive for varying periods up to 168 days.

No return of function was found beyond that of a "spinal" animal. Silver-stained sections of the spinal cord showed no evidence of any but the feeblest sort of regeneration. An exception to this was the invasion of the scar tissue by root fibers. Connective tissue invaded the space between the cord ends, but so feeble was the regenerative impulse that it was felt that the presence of the connective tissue was not of primary importance.

ALPERS, Philadelphia.

CORTICOCORTICAL CONNECTIONS OF POSTERIOR WALL OF CENTRAL SULCUS IN MONKEY. O. SUGAR, L. V. AMADOR, and B. GRIPONISSIOTIS, J. Neurophysiol. **13**:229 (May) 1950.

The efferent connections of the cortex of the posterior bank of the central sulcus were investigated by physiological neuronography in the monkey (Macaca mulatta). This konicortex, histologically distinct from the homotypical cortex on the postcentral convolution, has strongest connections with the cortex just behind and in front of the central sulcus. The more inferior portions of the buried sensory cortex have strong connections with the cortex between the Sylvian and the intraparietal sulci. The mild firing into the posterior end of the superior temporal sulcus is probably the surface extension of firing into the superior walls of the Sylvian fission, found by exploration after subpial resection of the superior temporal gyrus.

Feeble contralateral connections are localized to corresponding regions of the posterior bank of the central sulcus.

Except for meager connections with the cortex between the lower parts of the arcuate and central sulci, and those in the posterior part of the superior temporal gyrus, the connections of the sensory koniocortex of the central sulcus do not differ greatly from those of the surface of the postcentral gyrus.

No connections were found between the posterior bank of the central sulcus and the cortex behind or below the superior temporal sulcus or, with one minor exception, in front of the arcuate sulcus.

ALPERS, Philadelphia.

TRIGEMINAL NEUROTOMY AND BLOOD PRESSURE RESPONSES FROM STIMULATION OF LATERAL CEREBRAL CORTEX OF MACACA MULATTA. P. D. WALL and K. H. PRIBRAM, J. Neurophysiol. **13**:409 (Nov.) 1950.

For many years blood-pressure responses obtained from stimulation of various areas of the cerebral cortex have been the subject of considerable attention. This study is an attempt to ascertain the entire extent of the lateral neocortex from which these responses are obtainable by using the stimulating techniques now available, and to begin the investigation of whether or not a common mechanism links these various areas.

Blood-pressure responses of a magnitude greater than 10 mm. Hg which resulted from stimulation of the cortex of subjects whose trigeminal nerve was intact showed that the responsive cortex was far more extensive than had previously been reported. The responses varied, but they were invariably obtained from the region around the dorsal part of the central fissure, extending forward above the superior limb of the arcuate sulcus and the cortex lying below the inferior limb of the arcuate sulcus, especially toward the Sylvian fissure. In some animals responses were consistently obtained from other regions, such as the anterior bank of the lunate sulcus, the angular gyrus, and the inferior occipital regions. The responses produced by stimulating the motor area did not depend on movement produced, since the blood-pressure changes persisted after all movements had been inhibited by curare.

It was noted that many of the responses were maximal when areas around cortical blood vessels were stimulated. Since similar responses were obtained from dural stimulation, which has a trigeminal innervation, trigeminal-nerve sections were carried out. After this procedure had been carried out unilaterally in four animals, the denervated and the normal side were stimulated alternately and the results compared. The side which had not been denervated showed the pattern of response already described. On the denervated side, however, blood-pressure responses were evoked from a very much more limited area. After trigeminal-nerve section, stimulation of any part of the homolateral cortex did not lead to a rise in blood pressure.

The most likely explanation of the effect of trigeminal-nerve section on the responsiveness of the cortex is that afferent fibers from the cortical vessels have been interrupted. It is possible that an intact trigeminal nerve potentiates cortical responses to stimulation, either by an effect on cerebral circulation or by a direct neural synergism. However the effect of section of the trigeminal nerve is mediated, these results suggest that a separate autonomic mechanism involving the trigeminal nerve exists on the surface of the cortex.

ALPERS, Philadelphia.

TERMINATION OF SPINAL AFFERENTS TO INFERIOR OLIVE IN CAT. A. BRODAL, F. WALBERG, and T. BLACKSTAD, J. Neurophysiol. **13**:431 (Nov.) 1950.

It is becoming increasingly evident that for a real understanding of the cerebellum and for a proper evaluation of the results of physiological studies a detailed knowledge of the origin and termination of the cerebellar-fiber system is indispensable. This paper deals with one of the many important gaps in our knowledge to be filled, namely, the termination of the spino-olivary fibers.

Lesions were made at various levels of the spinal cord in 20 cats. The lesions involved different funiculi and/or the dorsal horns. The ensuing degeneration of terminal fibers and *boutons* in the inferior olive were studied in silver preparations. The principal findings are summarized as follows:

1. The spinal fibers to the inferior olive ascend in the ventral funiculus, and some also in the adjoining part of the lateral funiculus. They appear to originate from all levels of the cord.

2. Somewhat more than half the fibers cross in the medulla spinalis.

3. The fibers terminate by means of typical *boutons* on the perikarya and on the end processes of the cells in certain parts of the inferior olive. Most, if not all, terminal fibers are collaterals of ascending fibers.

4. The bulk of the spino-olivary fibers reach the ventrolateral part of the dorsal accessory olive and the ventrolateral part of the caudal half of the medial accessory olive. Some fibers pass to two distinct small parts of the olive: the nucleus β and the dorsomedial cell column, and a number to the dorsal cap.

5. Spinal impulses are distributed by means of the olive in great numbers to the vermis of the anterior lobe, some to the pyramis, a few to the uvula and the declive, and still fewer to the nucleus fastigii.

6. The fibers from the cervical and upper thoracic portions of the cord are far scantier than those from the lumbosacral portion. There is some indication that the number of fibers from the cervical and upper thoracic portions reaching the olivary areas which project on the lobulus centralis are even scantier than those passing to the olivary areas which send their fibers to the culmen. The authors suggest that the spinocerebellar pathway through the external cuneate nucleus (commonly considered the cervical-cord equivalent of Clarke's column) may represent an accessory pathway also for the spino-olivocerebellar system from higher levels of the cord.

7. The spino-olivocerebellar pathway, in its organization, presents a striking similarity to the dorsal spinocerebellar tract. The only difference appears to be that the impulses transmitted through the olive reach the vermis of the anterior lobe only, while the fibers of the dorsal spinocerebellar tract terminate also in the intermediate parts of the anterior lobe. Together with other differences in fiber connections, this emphasizes the importance of considering the subdivisions of the anterior lobe into three longitudinal zones.

8. The anatomical findings tend to show that the "spinal" areas of the inferior olive function purely as relay stations. Impulses mediated through the spino-olivocerebellar pathway will reach the cerebellum later than those passing in the dorsal spinocerebellar tract. The similarity in the organization of these two systems indicates a similarity in function. For anatomical reasons, the spino-olivocerebellar system cannot be supposed to mediate tactile impulses to the cerebellum. The findings in this study emphasize the necessity of considering the functional subdivision of the inferior olive in physiological experiments.

ALPERS, Philadelphia.

SOME FUNCTIONAL CONNECTIONS BETWEEN HYPOTHALAMUS AND MEDULLA. W. C. THOMPSON, and L. M. N. BACH, J. Neurophysiol. **13**:455 (Nov.) 1950.

This investigation was concerned with the elicitation of effects on blood pressure, respiration, and the knee jerk by stimulation of the lateral parts of the posterior hypothalamus, followed by interruption of the presumably hypothalamicofugal tracts in the medulla, and a study of the altered responses.

Preliminary stimulus-mapping of the posterior hypothalamus showed a pattern response similar to that described earlier for vasomotor responses, but, in addition, respiration and somatic reflexes were found generally to vary in the same direction as the blood-pressure responses.

Interruption of the medial (inhibiting) reticular formation in the medulla served to enhance hypothalamic facilitation of vasomotor, respiratory, and somatic reflexes. Interruption of the dorsolateral (facilitatory) reticular formation resulted in depression or abolition of hypothalamically induced facilitation of vasomotor, cardiac, respiratory and somatic reflexes. Simultaneous stimulation of the bulbar inhibitory system opposed hypothalamically induced vasopressor responses to the same extent that uncomplicated stimulation of this system caused vasodepression.

Further evidence is presented to indicate that the bulbar facilitatory and inhibitory systems, activated by the posterior hypothalamus, influence vasomotor, respiratory, and somatic activity in the same direction.

ALPERS, Philadelphia.

SPIKE DISCHARGES OF SINGLE UNITS IN THE CEREBELLAR CORTEX. J. M. BROOKHART, G. MORUZZI and R. S. SNIDER, J. Neurophysiol. **13**:465 (Nov.) 1950.

This report describes an attempt to record the spike discharges of intrinsic cerebellar neurons by leading with microelectrodes from the different layers of the cerebellar cortex. Spike potentials of single units were recorded from the cerebellar cortex of decerebrated or anesthetized cats through the use of fine-wire microelectrodes, which circumvent the detrimental influences of cerebellar movement and pressure that make use of rigid electrodes unsatisfactory.

Intrinsic cerebellar neurons were found to be spontaneously active at frequencies ranging from 20 to 125 cps, with the majority falling in the range of 70 to 80 cps. This activity occurred in erratic bursts of variable length, separated by silent intervals of variable duration. Factors controlling the resting frequency and the timing of the periods of activity and silence were not determined.

The identity of the unit producing this activity is unknown. Activity in intrinsic units may be differentiated from activity in extrinsic, or afferent, units through the local use of strychnine and through differences in the responses of the two types of units to sensory stimulation. The intrinsic units were active in animals with chronic surgical isolation of areas of the cerebellar cortex.

Local application of strychnine to the cerebellar cortex produced characteristic convulsive, avalanching outbursts of activity in intrinsic cerebellar neurons. Similar patterns of activity were also produced by other forms of intense stimulation.

The authors describe some responses of cerebellar neurons to afferent volleys over spinocerebellar paths and over corticopontocerebellar paths. They have found it possible to evoke, to augment, and to inhibit activity in cerebellar neurons by such afferent stimulation.

ALPERS, Philadelphia.

LOCALIZATION OF CORD TUMORS BY ELECTROMYOGRAPHY. P. F. HOEFER and S. M. COHEN, J. Neurosurg. **7**:219 (May) 1950.

Localization of tumors of the spinal cord by electromyography was attempted in 88 cases with 91 verified lesions. Precise levels were established by this method in 83.1% of 83 lesions considered localizable. In the cases of eight other lesions found at operation or autopsy to be multiple or widespread, the electromyographic method had indicated their diffuse nature. Hoefer and Cohen found electromyography to be superior to all other methods employed for localization in their series of cases.

ALPERS, Philadelphia.

Neuropathology

MORTAL BRAIN WOUNDS: A PATHOLOGICAL STUDY. E. CAMPBELL and H. KUHLENBECK, J. Neuropath. & Exper. Neurol. **9**:139 (April) 1950.

The present study of fatal brain wounds was undertaken during the Italian campaign for the principal purpose of collecting data which might be of help in the early recognition of fatal injuries. This, in turn, presented an unusual opportunity to observe chronologically the histologic changes which followed missile injuries and to examine the varieties of fracture which occurred.

The study was limited to the wounded who survived long enough to reach a forward hospital. Twenty-four cases were selected. The known survival times ranged from 30 min. to 10 days.

Injuries of the skull were of two principal types: first, the familiar depressed fractures, often accompanied with fragmentation of both bone and missile; and, second, "discontinuous" fractures, which occurred principally in the base of the skull and which were found in 9 of the 24 cases. The latter were commoner in the region of the cribriform plates and orbital roofs; thus, they may be associated with neural damage at a distance from missile tracts and, in addition, may open pathways for the entrance of infection or air into the cranial cavity.

The ventricular system was wounded in three-fourths of the cases; the amount of intraventricular hemorrhage varied widely. The pathway of the missile was commonly ragged, and was often made multiple by fragmentation of both bone and metal particles. The neural destruction of neural tisssue in the walls of the tract was not uniformly discernible immediately but became so many hours later, when softening had taken place. Such areas are believed to correspond to the "zones of delayed disintegration" of Rand and Courville.

Hematomas were common and frequently large in wound tracts, particularly in the ventricles if the latter had been injured. Extradural clots were usually present but rather small; subdural hematomas were likewise common, but large only in a few instances.

The cellular reaction of the brain tissue to trauma is more sluggish by far than the tissues in other organs. The reactive processes during the early stages following injury, as studied in this series, were carried out chiefly by the mesodermal components, while the ectodermal elements

showed only a limited activity. These reactive changes, in which polymorphonuclear leukocytes predominated, may be designated as traumatic encephalitis. In the first stage, from the first to the third day, degenerative processes and edema were accompanied by infiltration with hematogenous mesodermal elements. In the second stage, from the fourth to the 10th day, proliferation of capillaries marked the beginning of a reparative process, and compound granular corpuscles appeared in increasing number.

ALPERS, Philadelphia.

Psychiatry and Psychopathology

TOXIC PSYCHOSIS DUE TO PROPHENPYRIDAMINE (TRIMETON®). A. R. YAPALATER and F. V. ROCKWELL, J. A. M. A. **143**:428 (June 3) 1950.

The case reported is believed to be the first instance of a toxic psychosis following prolonged medication with the antihistamine drug prophenpyridamine (trimeton®). The patient, a robust high-school graduate aged 18, was subject only to allergic rhinitis, which became more distressing while he was working on a farm during the summer. He was given prophenpyridamine tablets, each containing 25 mg., three times a day. Over a two-month period the patient ingested 200 such tablets, until the onset of the present illness.

Psychiatric examination disclosed that the patient was obviously lethargic and mentally confused. In general, psychomotor activity was much retarded. Physical examination disclosed a blood pressure of 160 systolic and 108 diastolic and a depressed respiratory rate, varying from seven to 10 a minute. The lethargy, impaired coordination, and depressed respiration rate were believed to be due to central respiratory inhibition.

On the eighth day of hospitalization his symptoms began to clear, and he remained well until his discharge, five weeks later.

Experimentally, the patient was given therapeutic doses of chlorprophenpyridamine maleate (chlortrimeton), and this produced significant electroencephalographic changes within three days. Yapalater and Rockwell point out this observation may be of significance for further investigation.

ALPERS, Philadelphia.

Meninges and Blood Vessels

MULTIPLE SUBDURAL HEMATOMAS IN AN INFANT. J. M. WILLIAMS, Am. J. Dis. Child. **80**:970 (Dec.) 1950.

The molding of the head as it passes through the birth canal is a well-known fact. When biparietal pressure is exerted on the cranium, there is a tendency for the brain itself to be displaced downward. Since the longitudinal (sagittal) sinus is supported by the upper margin of the parietal bone, it cannot ordinarily accompany the brain when this displacement occurs. Consequently, the central veins will be stretched and may rupture. In the case of multiple subdural hematoma here reported another mechanism in the formation of subdural clots was observed.

The patient was a white baby, born at full term, after a labor totaling five hours; delivery was by low forceps with episiotomy. No abnormalities were noted at the time of his discharge from the hospital, one month later. At the age of 3 mo. the baby was examined and found to have large, tense fontanels; the eyes turned downward; the general physical condition was good, and the mentality appeared normal. No history of any injury was obtained. He was admitted to the hospital with a diagnosis of subdural hematoma.

At operation three subdural hematomas of apparently progressively graded increasing ages were found on the left side and four on the right. Fluid reaccumulated after operation and was aspirated twice. Two weeks after operation, the patient suddenly became pallid and cyanotic and died shortly thereafter.

On review of the operative and autopsy observations, it appeared that this child had repeated subdural hematomas, each one apparently independent in time of the others. The encapsulated hematomas most closely applied to the brain were the oldest, while the hemorrhages appeared progressively more recent, judged by the color of the fluid, as they approached the skull. The

vessel probably responsible for the hemorrhage on the left was later identified as one of the central veins. The vessel on the right presumed to be responsible was not clearly identified.

The extensive thromboses of the dural sinuses probably contributed to the repeated hemorrhages by the increased intrasinus pressure caused by their presence. These thromboses undoubtedly had their origin as marantic thrombi induced in the longitudinal sinus after the first hemorrhage that had gradually filled most of the dural sinuses over the convexity. In such circumstances, the venous pressure within the cortical veins was bound to rise, and this, plus a trivial jar, was sufficient to "blow out" the scarred and weakened junction of the veins and the sinus.

Williams notes that this case clearly reveals the commonest origin of the formation of subdural hematomas and suggests that the appearance of symptoms after a long latent interval may be due not solely to increase in the size of the clot by osmosis but to subsequent hemorrhage either into, or on top of, the original clot. Sinus thromboses may abet such a process. Finally, late appearance of symptoms can result from a seemingly trivial injury.

ALPERS, Philadelphia.

NEUROLOGICAL MANIFESTATIONS ASSOCIATED WITH DISSECTING AORTIC ANEURYSM. F. P. MOERSCH AND G. P. SAYRE, J. A. M. A. **144**:114 (Dec. 2) 1950.

This study consisted of an analysis of data on 26 cases of verified dissecting aneurysm of the aorta. There were available for study the dissected aortas in the 26 cases. In addition, the brains in 12 cases, the spinal cords in 9 cases, and portions of the sciatic nerves in 9 cases were studied. The aortas were studied to determine the location and extent of the dissection and to correlate the involvement of the aortic branches with possible interference with the vascular supply of the central and peripheral nervous systems.

Major neurological complications appeared in 12 cases. The major number, 8, were of cerebral origin. In 5 of these 12 cases there were definite signs of hemiplegia. It is well to bear in mind that not every hemiplegia occurring during the course of the illness need be due directly to the dissection, but that hemiplegia may result from other, unrelated factors. In 3 cases symptoms were of spinal-cord origin, in 1 being transverse myelitis and in the other 2 weak legs and changes in reflexes. In 1 case it was difficult to determine whether the clinical findings represented damage to the cerebrum or the spinal cord damage, as the patient showed confusion, pains, and paresthesias of the leg. In 8 cases presented multiple neurological signs were present.

While pain was the usual signal ushering in the train of symptoms, other, equally dramatic warnings gave notice of the impending disaster. Thus, the initial symptom or symptoms were pain and unconsciousness in two patients, pain and convulsions in three patients, hemiplegia in two patients, and vertigo in one patient.

The neurological complications tend to follow the definite patterns of cerebral, spinal cord or peripheral nerve origin. Frequently the neurological symptoms may be diffuse, involving all portions of the nervous system. In this series 46% of the patients gave evidence of neurological complications. Involvement of the peripheral nerves was essentially negligible, although it must be pointed out that only portions of the sciatic nerves were available for examination. The cerebral manifestations are exceedingly variable and can usually be explained on an anatomicopathologic basis.

The more important points to be considered in establishing a correct diagnosis are as follows: (1) the sudden onset of symptoms, with prostration or collapse; (2) the presence of severe, and usually prolonged and migratory pains; (3) the presence of hypertension; (4) the presence of neurological symptoms; (5) normal to only slightly elevated temperature; (6) an enlarged heart with a cardiac murmur and transitory pericardial rub; (7) an electrocardiogram which is not diagnostic; (8) roentgenographic findings of enlarged heart with tortuous aorta which may be dilated and calcified; (9) increased leucocyte count, and (10) albumin in the urine, as well as red blood cells at times.

ALPERS, Philadelphia.

MENINGIOMAS OF THE SPHENOIDAL RIDGE. E. D. HORNING AND J. W. KERNOHAN, J. Neuropath. & Exper. Neurol. **9**:373 (Oct.) 1950.

This survey comprises 64 cases of tumors of the sphenoidal ridge. The clinical records and findings were studied, and an attempt was made to correlate the data with the histologic structure of the several tumors.

The lesions were divided into three main groups according to the point of origin from the inner, middle, or outer third of the sphenoidal ridge. The tumors arising from the outer third were further divided into tumors *en plaque* and global tumors. Twenty-five patients in this series first came under observation during the fifth decade of life. An almost 4:1 ratio of women to men obtained. Twenty-nine tumors originated from the inner third part of the ridge; 15, from the middle third part, and 20, from the outer third part, 8 of which were tumors *en plaque* and 12 were global tumors. Cytologic studies identified 48 tumors as meningotheliomatous meningiomas, 6 as psammomatous meningiomas, 6 as fibroblastic meningiomas, 2 as mixed tumors, and 2 as unclassified.

Tumors of the inner third part of the sphenoidal ridge produced headache as the first presenting symptom in eight cases and visual failure as the first sign in seven cases. Bilateral choked disk was seen in four cases, proptosis in four cases, personality changes in five cases, and anosmia in three cases.

Symptoms caused by tumors of the middle part of the sphenoidal ridge were found to be somewhat inconstant. Personality changes were evident in eight cases, and anosmia was present in five cases. Bilateral choked disk was seen in six cases and proptosis in three cases. Proptosis was present in six cases of tumors *en plaque* of the outer third part of the sphenoidal ridge. The global type of tumor in this part of the ridge caused bilateral choked disk in three cases and proptosis in seven cases.

ALPERS, Philadelphia.

Diseases of the Brain

MENINGOTHELIAL MENINGIOMA OF THE FOURTH VENTRICLE. F. S. VOGEL and L. D. STEVENSON, J. Neuropath. & Exper. Neurol. **9**:443 (Oct.) 1950.

Vogel and Steveson report a case of meningioma of the fourth ventricle. In this case, unlike the two cases previously studied by other investigators and reported in the literature, the tumor was an incidental finding at autopsy in the brain of a man, aged 65, who died of carcinoma of the stomach. There had been no complaints referable to the lesion in the central nervous system, and several neurological examinations during the terminal few weeks gave no indication of its presence.

The tumor on microscopic study proved to be a meningothelial meningioma. It was clearly shown by topographical study to have arisen from the tela choroidea, a structure more probably of pial than of mixed pial-and-arachnoid composition. The tumor contained cells histologically identical with the meningothelial cells which figure prominently in the neoplasms ascribed to the arachnoid membrane.

These facts suggest that the pia mater and arachnoid, having a common embryonic origin, share the potentiality of forming a class of neoplasms that is morphologically indistinguishable.

ALPERS, Philadelphia.

THE ELECTROENCEPHALOGRAM IN SUBDURAL HEMATOMA, WITH A REVIEW OF THE LITERATURE AND THE PRESENTATION OF SEVEN CASES. G. W. SMITH, W. H. MOSBERG, E. T. PFEIL and R. H. OSTER, J. Neurosurg. **7**:207 (May) 1950.

The pathology and treatment of subdural hematoma are well understood, but the clinical picture is subject to great variation. The encephalogram offers a new and different approach in that alteration in the physiologic (electrical) activity of the brain can be studied directly, as well as indirectly. With subdural hematoma the abnormalities in electrical activity of the brain are shown to be altered dependent on (1) the amount of the bleeding, (2) the location, and (3) the time interval between the bleeding and the electroencephalographic recording.

Smith and his colleagues report seven cases of surgically proved unilateral chronic subdural hematoma, with their electroencephalographic patterns. Except for two, these cases are clinically

and surgically instances of "pure" chronic subdural hematomas, with no recurrent contusion or laceration of the brain.

The preoperative electroencephalogram was characterized by a marked generalized asymmetry in the activity of the hemispheres, the hemisphere underlying the hematoma showing decreased amplitude and random low-voltage slow waves. This pattern is representative of tracings of "pure" chronic subdural hematoma.

It is the authors' opinion that the variations in the electroencephalograms of subdural hematoma can be explained by the presence of concomitant intracranial hemorrhage and/or damage to the brain. Failure to take a bipolar tracing with the recording electrodes over the site of the hematoma will result in an "atypical" record. They point out that the electroencephalogram is a diagnostic aid, and is to be used only as an adjunct to the history, clinical findings, and observation.

ALPERS, Philadelphia.

LONGEVITY OF PATIENTS WITH GLIOBLASTOMA MULTIFORME. M. G. NETSKY, B. AUGUST and W. FOWLER, J. Neurosurg. **7:** 261 (May) 1950.

The almost uniformly short life span of patients with glioblastoma multiforme is well known. In a review of gliomas by Netsky and his co-workers, a few cases were encountered in which duration was so long that they are recorded here. In a series of 70 verified cases, the survival period in five was six years or longer from the time of the first symptom, the longest being 14 yr.

An analysis of factors in survival revealed that operation had no significant effect on longevity; irradiation, a slight effect, if any. The longest survivals occurred in cases with onset at the 24 to 42 yr. of age. However, age at onset was not a constant prognostic factor. The sex of the patient, the location of the neoplasm, and the histologic appearance gave no indication as to longevity. A significant lengthening of survival was found in cases in which the initial symptom was a focal motor seizure. While this was generally true, some patients with this symptom had a short survival.

The authors conclude that at present there is no means, clinical or histologic, of predicting in a given case which patient will survive longer than the average.

ALPERS, Philadelphia.

Diseases of the Spinal Cord

RELATION OF SPINAL CORD DISEASE TO GYNECOMASTIA AND TESTICULAR ATROPHY. I. S. COOPER, E. H. RYNEARSON, A. A. BAILEY, and C. S. MACCARTY, Proc. Staff Meet., Mayo Clin. **25:**320 (June 7) 1950.

Mammary enlargement and testicular atrophy among young men who have sustained a severe injury to the spinal cord have been observed by several investigators, and they have suggested that there may be a causal relation between injury to the spinal cord and the subsequent development of gynecomastia in some paraplegic men. Although gynecomastia and testicular atrophy have previously been reported as secondary to traumatic lesions of the spinal cord, the authors here record observations on two patients who had gynecomastia associated with degenerative lesions on the spinal cord.

Gynecomastia, testicular atrophy, and decreased urinary excretion of 17-ketosteroids were noted in the case of a man aged 21 who had Friedreich's ataxia (hereditary sclerosis, spinal form). Mammary enlargement also was observed in the case of a man of 45 who had syringomyelia of the upper cervical portion of the spinal cord. In addition, advanced atrophy of the seminiferous tubules, with aspermatogenesis associated with hypertrophy of the interstitial cells of the testis, were observed in two cases of syringomyelia at autopsy.

The occurrence of gynecomastia and testicular atrophy in patients having degenerative diseases of the spinal cord is considered significant, for the following reasons: (1) It has been hypothesized that the spinal cord conducts nerve impulses from the brain which have a trophic influence on the testis, particularly on the seminiferous tubules and spermatogenesis; (2) the phenomenon provides data which can be compared with similar changes in men who are paraplegic owing to traumatic lesion of the spinal cord, and (3) it has clinical implications in regard to adjuntive medical treatment in various diseases of the spinal cord.

ALPERS, Philadelphia.

Peripheral and Cranial Nerves

SEVERE POLYNEURITIS FOLLOWING GOLD THERAPY FOR RHEUMATOID ARTHRITIS. J. B. DOYLE and E. F. CANNON, Ann. Int. Med. **33**:1468 (Dec.) 1950.

Reactions during the course of treatment of rheumatoid arthritis with gold are frequent. In a series of 964 complications (Sundelin), 107 involved the nervous system. In most instances the symptoms suggested damage to the brain and associated structures. In 10 cases the evidence indicated involvement of the peripheral nerves alone.

In most cases, involvement of the peripheral nerves is accompanied with severe pain of boring, burning, or lancinating type, which is often paroxysmal. The neurological symptoms may range from the slightest to the severest, and they may arise from the brain, spinal cord, neural plexuses, or peripheral nerves. The symptoms may be purely subjective; or they may be characterized by epileptiform seizures, delirium, and coma, or by transient or relatively persistent evidences of polyneuritis, with paresthesias, weakness or paralysis of the limbs, loss of common and deep sensation, and diminution or loss of the superficial and deep reflexes. Vasomotor changes of transitory nature are frequent.

The authors report a case of severe polyneuritis occurring in the course of therapy of rheumatoid arthritis with gold sodium thiomalate (myochrysine®). The patient was treated over a period of two months with weekly injections of 100 mg. of gold sodium thiomalate until 900 mg. of the drug, or 450 mg. of gold, had been given, with what were considered very satisfactory therapeutic results. At about the middle of this course he had had a mild rash and transient itching. Three days after the last injection the patient awakened with tingling and prickling of the hands, wrists, feet, and ankles, which gradually grew more pronounced. Paresthesias progressed proximally; the patient became bedridden by the third week, and he became unable to feed himself. There was difficulty in starting the urinary stream by the fourth week, but immediately after this improvement began, and when he was seen, five weeks after onset of symptoms, the girdle sensations had almost disappeared and control of the hands was better.

Neurological examination at this time showed slight to moderate weakness of the upper and lower extremities.

A diagnosis of multiple peripheral neuritis with unusual characteristics was made. The girdle sensations, the feelings of constriction around the limbs, the involvement of the urinary sphincters, and the aberrant colloidal gold curve were suggestive of involvement of the nerve roots, and possibly of the spinal cord. Hygienic measures, active and passive movements, and graduated activities were prescribed. The patient continued to show steady and rapid improvement. Four months after the onset of polyneuritis he was free from paresthesias and weakness. At times he was troubled by twitching of the arm musculature. A complete neurological examination at this time revealed no abnormality.

ALPERS, Philadelphia.

Treatment, Neurosurgery

USE OF PHENURONE IN CONVULSIVE DISORDERS IN CHILDREN. H. M. KEITH, Am. J. Dis. Child. **80**:719 (Nov.) 1950.

Keith reports on a series of 35 patients (34 children, 1 adult) who had convulsive disorders and were treated with phenacemide (phenurone®). All these patients had been treated with other drugs, singly or in combination, and in varying amounts. The phenacemide was given because the attacks were not otherwise controlled.

Of the 35 patients observed for three months or more, 8 (23%) have been entirely free from attacks for periods of three to 17 mo. Fifteen patients (43%) have been improved, and 12 have not been benefited. Thus, 23 patients have had a decided reduction in the number of attacks or have been entirely free from convulsions while taking phenacemide.

Phenacemide may be used in combination with other anticonvulsants. In common with most drugs, however, it may produce unfavorable side reactions, mainly dermatitis medicamentosa, unfavorable personality disturbances, and, in rare cases, disturbance of liver function. When used with suitable precautions, it appears to be a useful addition to the list of anticonvulsant drugs.

ALPERS, Philadelphia.

RAPID ATTAINMENT OF THERAPEUTIC PENICILLIN CONCENTRATIONS IN THE CEREBROSPINAL FLUID. W. P. BOGER and W. W. WILSON, Am. J. M. Sc. **27**:593 (June) 1949.

Boger and Wilson administered 500,000 units of penicillin in aqueous solution intravenously to 18 unselected patients with dementia paralytica and examined the spinal fluid two and three hours after the injection. At the end of two hours demonstrable concentrations of penicillin in the cerebrospinal fluid were found in 14 of the 18 patients, and at three hours, in 15 of the 18 patients. When the same dose of penicillin was administered with 3 gm. of carinamide, penicillin appeared in the cerebrospinal fluid at the end of two and three hours in all the 18 patients. The plasma concentrations resulting from the administration of penicillin were increased by carinamide from two to five times, and the cerebrospinal-fluid concentrations were doubled. The authors conclude that the parenteral, particularly the intravenous, administration of penicillin has a place in the therapy of purulent meningitis, and that intrathecal injection of penicillin is unnecessary in the majority of patients.

MADOW, Philadelphia.

TREATMENT OF PERIPHERAL NEUROPATHY IN DIABETES MELLITUS. W. S. COLLENS, A. M. RABINER, J. D. ZILINSKY, L. C. BOAS, and J. J. GREENWALD, Am. J. M. Sc. **219**:482 (May) 1950.

This paper is concerned with a report of quantitative studies on impaired vibration sense in cases of diabetes mellitus and with an evaluation of the use of vitamin-B complex and some of its fractions as supplements in the treatment of diabetic neuropathy. The authors report 68 cases of diabetes with symptoms of peripheral neuritis in which quantitative studies of vibration sense were made before and after the institution of treatment with vitamin-B fractions. It was found that 60% of the patients showed improvement in vibration sense, some even a return to normal. Actual subjective relief was attained in 72%.

Collens and his co-workers studied 51 cases of diabetes in which there was reduced vibration sense without symptoms of peripheral neuropathy. Analysis showed improvement in readings after the institution of treatment in 70%.

Quantitation of the threshold of response to stimulation of vibration sense has served to stress the recognition of the wide incidence of neuropathy in diabetes mellitus and to evaluate therapy. The use of the clinical vibrometer has made it possible to recognize reversibility in impairment in vibratory sense after treatment and to anticipate functional recovery in nerves with improvement in the clinical symptoms of the neuropathies. This instrumental technique has also served to evaluate therapy in the neuropathies and to establish the dose of vitamin-B complex and its supplements.

ALPERS, Philadelphia.

Congenital Anomalies

DEAFNESS AND KERNICTERUS. R. N. BARNETT and C. F. RYDER, Arch. Otolaryng. **52**:771 (Nov.) 1950.

Kernicterus is the most dreaded late complication of hemorrhagic disease of the newborn. This is manifested pathologically as more or less symmetrical yellow pigmentation of the basal ganglions and certain brain nuclei, associated with severe cellular damage, and clinically as motor abnormalities and varying degrees of permanent retardation. Deafness has never been described as one of the sequelae.

The authors report a case of complete deafness accompanying the other sequelae of severe kernicterus. The baby was treated with exchange transfusions performed 48 hr. after birth. At the time of the report, at 14 mo. of age, there was pronounced brain damage, evidenced by deafness and profound general retardation. The importance of this case lies in the recognition of an added hazard in treating babies with this condition.

ALPERS, Philadelphia.

Society Transactions

CHICAGO NEUROLOGICAL SOCIETY

Joseph A. Luhan, M.D., President, in the Chair

Regular Meeting, Feb. 13, 1951

Brain-Stem Lesion of an Unusual Type. Dr. Alex J. Arieff and Dr. Norman B. Dobin.

The authors presented a case of a brain-stem lesion of vascular origin at the level of the pons in a man aged 47, with a history of syphilis and current hypertension. The patient had two successive lesions, one involving the left side of the brain stem, manifested by transient paresthesia and paresis of the right side of the body. The second involved the right side of the pons at the level of exit of the abducens nerve, implicating the corticospinal and corticopontile tracts, the medial lemniscus, the spinothalamic tract, the abducens nerve, the reticular substance, and the trapezoid body. It was manifested by hemiparesis, loss of all sensory modalities and severe ataxia on the left side of the body, and, on the right side, by Horner's syndrome and transient paralysis of the external rectus muscles, with dysarthria, dysphagia, and diminished auditory acuity. The severe ataxia, and involuntary movements occurring on the side opposite the lesion, associated with almost complete loss of sensation on that side, were believed to be due to sensory ataxia, simulating ataxias resulting from high lesions of the cervical portion of the cord and the parietal lobe.

DISCUSSION

Dr. Louis Berlin: I have seen the patient several times. There was a period during his illness when he experienced what he described as a sensation of "holding on to a high-tension wire." This lasted only several days at a time. At other times, he had pins-and-needles sensations in the left hand. There is a history of a stroke on the right side. Then there occurred a second apoplectic episode, after which there were paroxysmal pains in the left upper extremity and independent movements of the extremity. Some of you may have noted the involuntary athetoid movements of the left hand. There were also hemihypalgesia, hemiataxia, and mild hemiparesis. It is my impression that this picture constitutes more than a brain stem syndrome. I believe that there is a lesion in the region of the thalamus. The variation in the intensity of this patient's pain is in accord with Dejerine's comment (Dejerine, J.: Semiologie des affections du systeme nerveux, Paris, Masson & Cie, 1926). I have seen thalamic syndromes in which the pathologic process was not limited to the thalamus. For example, it is well known that one may have a hemianopsia with the thalamic syndrome. I had a case of anosognosia with this syndrome. The patient believed that his brother's arm was sewn on to his left shoulder and experienced pains in his "brother's" arm. Another patient combined this syndrome with a frontal-lobe syndrome. He complained of almost continuous, unremitting pain when he was questioned; yet he never sought analgesics and always smiled as he stated that the severity of his pain never varied. The patient reported here, I suspect, has a lesion in the region of the right thalamus and a lesion of the brain stem responsible for the Horner syndrome. All the recent changes can be explained by a lesion on the right side due to involvement of the posterior cerebral artery and its perforating branches.

Dr. Alex Arieff: Everyone is entitled to his opinion as a clinician. I, too, examined the patient, but not as early as my associates. This patient's symptoms started with paralysis of the sixth cranial nerve. This symptom, we feel, indicates the level of the lesion. The patient was questioned intensively concerning his pain. It was our impression after this that his pain was actually due to a cramp in his left arm accompanied with a surging sensation and roaring in his ears. The severe ataxia on the left side, because of its exaggeration on intention, seemed to me to be cerebellar in origin, but such a lesion could not explain the picture of left hemiplegia and hemianesthesia on the same side. Because of this, I suspected that the lesion was higher up in the midbrain, involving the red nucleus. The absence of third-nerve involvement ruled out

this possibility. If the lesion were higher in the thalamus, he should have visual-field disturbances, which he does not have. Because this severe ataxia is due to absence of sensation, it is an unusual type. It is seen in lesions of the cervical portion of the cord and the parietal lobe.

DR. JOSEPH A. LUHAN: I am familiar with this case because the patient was assigned to my service. I believe that the most interesting feature of the case is the problem of differential diagnosis concerned with localization of the lesion relating to the ataxia—ataxia which is contralateral with respect to certain other symptoms (such as the Horner syndrome) which occur on the side of a brain-stem lesion. The differential diagnosis is concerned, therefore, with "posterior-column ataxia," contralateral to interruption of the medial lemniscus, on the one hand, or with ipsilateral "cerebellar ataxia," on the other. If we accept the first of these alternatives, a lesion chiefly on one side of the brain stem will account for the clinical picture, whereas if the ataxia is of cerebellar nature, two lesions, one on the right side and the other on the left side of the brain stem, would more satisfactorily explain the clinical picture.

There was some question whether this patient suffered from pain such as occurs in the thalamic syndrome. I have seen him in the ward when he complained of surges of pain in the left upper extremity like the shock from a brisk electric current. However, spontaneous pain and painful dysesthesias do not compel one to assume a thalamic or a juxtathalamic lesion to explain them. I have seen patients with the Wallenberg syndrome who experienced distressing spontaneous central pain.

DR. ALEX ARIEFF: If the pain was not caused by cramps, it might be due to stimulation of the sensory pathways, similar to the type of pain seen in paraplegics in whom we have found pain due to stimulation of the proximal end of the spinal cord, perhaps as the result of scar formation. I do not believe that the type of pain this man has is thalamic in origin, for the reason cited. That it is sensory pain in the presence of anesthesia we agree.

DR. JOSEPH A. LUHAN: This spontaneous central pain is not necessarily thalamic; but since this type of pain has been often noted and described in cases of thalamic lesions, one is apt to designate it carelessly as thalamic pain, just as certain types of sensory dissociation are commonly referred to as syringomyelic, regardless of the nature of the lesion.

Blindness on the Basis of Inattention: Report of a Case. DR. H. H. GARNER and DR. LOUIS BERLIN.

A man aged 62 had sustained two strokes in July, 1949. There followed slowing of all movements and impaired memory. There was mild hypertension, but physical examination otherwise revealed nothing abnormal. He had moderate organic dementia, but no aphasia, apraxia, or any type of sensory disturbance. There was quadriparesis, with a Parkinsonian tremor of the head and the left hand. Sucking reflexes and forced grasping were elicited on the right. The patient complained of being blind. He had a blank stare and did not respond to threatening movement; and when he was spoken to, his eyes wandered to the area of the sound. He could not identify objects with monocular vision, and with binocular vision he could not identify objects presented for less than five seconds. But with prolonged exposure to the visual stimulus he could identify a watch, cigarettes, a crucifix, or the picture of an automobile, and he could determine the color of these. The patient's appearance resembled the condition described in monkeys by Kennard and Ectors (Kennard, M. A., and Ectors, L.: Forced Circling Movements in Monkeys Following Lesions of the Frontal Lobes, *J. Neurophysiol.* **1**:45 [Jan.] 1938) after bilateral ablation of area 8 and extirpation of the frontal lobes.

DISCUSSION

DR. ALEX J. ARIEFF: I saw this patient when he was admitted to my service, and he appeared acutely ill and demented. My first impression was that of dementia paralytica. After further investigation his condition improved, and all the laboratory findings were within normal limits. I was not aware until recently that he had any vision whatsoever, and he presents an unusual clinical entity. I wonder whether his type of blindness is related to mind blindness.

DR. G. CLARK: Since visual disturbances are easily demonstrable in the macaque with appropriate frontal-lobe lesions, I have often wondered why comparable deficiencies are so infrequently seen clinically. Some time ago I studied a series of macaques with such lesions.

In most respects I was able to confirm Kennard's results, although I never saw anything resembling visual agnosia. With adequate lesions in a frontal visual field, a transient contralateral hemianopsia could be demonstrated, which lasted about three weeks. Food introduced into the ipsilateral field was rapidly and accurately snatched from a stick, and appropriate defensive responses were made to threatening stimuli introduced into that field. However, such objects in the contralateral field were completely disregarded. After bilateral lesions, the animals can pass a Poppelreuter test while still groggy from the anesthesia. However, the animal does this by means of head movements and grasps only objects directly toward its front. This loss in the peripheral portion of the visual fields is apparently very transient, and I have been unable to demonstrate any deficiency after 24 to 48 hr. I do not know whether such recovery is real or is made possible by increased utilization of head movements. During the acute phase after bilateral frontal ablation, there is thus at least a superficial resemblance to the condition of this patient. In both there is a loss in the peripheral portions of the fields, with maintenance of central vision much more pronounced in the animal.

DR. LOUIS BERLIN: I have not seen cortical blindness clinically. From what I have read, it is a true blindness in which the patient or the animal is not aware that he is blind. The patient may even deny his blindness. It is a sort of visual anosognosia. This patient does not show this type of defect. He does demonstrate something that Bender has emphasized (Bender, M. B., and Kreiger, H. P.: Visual Function in Perimetrically Blind Fields, A. M. A. ARCH. NEUROL. & PSYCHIAT. **65**:72 [Jan.] 1951), namely, that under various perimeters of stimulation, on exposure under different conditions of illumination and with prolonged stimulation, he was able to identify complex visual stimuli.

Epilepsy of Organic Origin: Report of a Case. DR. BEN W. LICHTENSTEIN and DR. STANISLAW MASLANKA.

J. V., a white man aged 24, was admitted to Cook County Hospital in October, 1950, because of convulsions. The patient had had seizures since the age of 7 yr. The seizures were both focal and generalized. The focal attacks consisted of myoclonic twitching of the right upper extremity, spreading over the right side of his body. There was an aura of flashes of colored light in the right field of vision. Physical examination revealed adenoma sebaceum of the face, a subungual fibroma on the fourth toe of the right foot, small gingival fibromas and a phacoma in the right fundus. A roentgenogram showed scattered calcifications in the brain. The diagnosis was tuberous sclerosis.

DISCUSSION

DR. JOSEPH A. LUHAN: Is the calcification centrally situated, perhaps in one of these candle gutterings on the ventricular surface, or in the cortex?

DR. BEN W. LICHTENSTEIN: There are both vascular and neuroglial formations in tuberous sclerosis, and in these roentgenograms one can see the hydrocephalus, the areas of increased density, and the nodules in the ventricular walls. What impressed me most were the gingival fibromas, which are easily overlooked. As you know, such cases are common in the institutions for the feebleminded.

Occlusion of the Basilar Artery: Clinicopathologic Report of Three Cases of Varying Duration. DR. JOSEPH A. LUHAN and DR. LEO A. KAPLAN.

CASE 1.—A white man aged 25, who had been diabetic for 10 yr., was admitted with inability to swallow, numbness and paralysis of the right side of the face, hypalgesia of the face (bilateral) and the left side of the body, and weakness of all extremities. Spinal-fluid pressure was 280 mm. of water, and the protein content, 78 mg. per 100 cc. The patient died 32 hr. after the initial appearance of neurologic symptoms. Necropsy revealed severe premature cerebral arteriosclerosis; recent thrombosis of the right vertebral artery, with the thrombus propagating into the basilar artery; pallor of the myelinated areas of the caudal portion of the pons; a small focus of ischemic necrosis in the retro-olivary region of the rostral portion of the medulla on the right, and similar foci in parts of the cortex of the right cerebellar hemisphere.

CASE 2.—A white man aged 45 collapsed while at work. He was stuporous, could not swallow, had dizziness, vomiting, and hiccups, and complained of incoordination in the left extremities

and of numbness of the left side of the face. There was a Horner syndrome on the left side. Two days later coma, fever and signs of diffuse cerebral irritation supervened. The patient died four days after onset of neurologic symptoms. Necropsy revealed thrombosis of the left posterior inferior cerebellar artery and of the proximal portion of the left vertebral artery, and partial thrombotic occlusion of the basilar artery. There was encephalomalacia of the left cerebellar hemisphere on its ventral aspect and of the retro-olivary region of the rostral part of the medulla on the left, without, however, any softening in the pons.

CASE 3.—A white woman aged 63, diabetic, became ill with generalized weakness, dizziness, vomiting, and slurring of speech 10 days before admission. In her stupor at the hospital, the Babinski sign was elicited bilaterally; nystagmus and weakness of the left side of the face were noted. Death occurred 15 days after onset of neurologic symptoms. Necropsy revealed advanced cerebral arteriosclerosis with thrombosis of the basilar and right posterior cerebral arteries. There was extensive anemic encephalomalacia in the caudal two-fifths of the pons and of the ventral surface of the left cerebellar hemisphere, and in the right occipital lobe.

The first two cases were of thrombosis in one vertebral artery complicated by propagation of the thrombus into the basilar artery, with fatal outcome before pontine encephalomalacia had time to develop. On the other hand, a case of thrombosis of the basilar artery of considerably longer duration was marked by extensive softening in the caudal portion of the pons.

DISCUSSION

DR. JOSEPH LUHAN: I do not know why the pons will withstand anoxemia from interruption of its blood supply so much longer than the cerebral cortex. Of course, it is not known how long there was virtually complete occlusion of the basilar artery in these cases. It is interesting that in the two cases with unilateral occlusion of the vertebral artery there was more softening in the cerebellum (on one side) than in the brain stem itself; this resulted from the shutting off of the blood supply to the posterior inferior and anterior cerebellar arteries on one side.

Lesion of the Brain Stem Due to a Stab Wound: Report of a Case. DR. IRVING C. SHERMAN and DR. ROBERT L. TENTLER.

A white man aged 27, a waiter, was the victim of stab wounds of the posterior thorax and a 2-cm. wound at the right basal occiput. Neurologic examination revealed spastic hemiplegia on the left side with hyperactive reflexes and pathologic toe signs on the same side. There was hemianesthesia of the left side of the body, with loss of deep pain, position and vibration senses. Pronounced dysmetria, adiadokokinesia and decomposition of movement were seen on the right. Undulatory nystagmus was present in all directions of gaze. Lateral gaze was lost bilaterally. The right pupil was smaller than the left, and there was sweating only on the left side of the face. The jaw protruded to the right. There was paralysis of the right side of the face, of peripheral type. Hearing was diminished on the right. The right half of the palate was paralyzed, and the patient had difficulty in speaking and swallowing.

Roentgenograms of the skull revealed no fracture; so entry of the weapon through the foramen magnum was postulated. A long lesion, localized on the right from the upper portion of the medulla to the rostral part of the pons, was suspected. Interruption of the pyramidal tract, medial lemniscus and longitudinal fasciculus explains the contralateral findings and the nystagmus. The cerebellar signs arise from severance of a cerebellar peduncle. The following cranial nerves were involved: both 6th nerves and the 5th (motor and sensory portions), 7th, 8th, 10th and 12th on the right side.

DISCUSSION

DR. ROBERT L. TENTLER: The lesion in this case seems to be fairly well localized to the right side of the brain stem. It is rather long, starting in the upper portion of the medulla and projecting into the pons to involve both abducens nuclei in the midline. The cerebellar peduncle and the lower cranial nerves were cut.

DR. H. R. OBERHILL: As I recall from the history, the neurologic symptoms developed several days after the injury. Am I right in assuming that the symptoms would appear that late? If they did, I should differ from the opinion that the patient's present neurologic picture is the result of a direct stab wound to the brain stem.

DR. ROBERT L. TENTLER: Apparently, the patient was so acutely ill when he was first examined that no one knew much about him except that he seemed to be dying.

DR. JOSEPH A. LUHAN: When he was in the ward some months ago, I was going to demonstrate him to a class as a case of a brain-stem lesion, but the signs he presented were so complicated that I thought the picture would confuse the medical students. Now, after some of the reversible circulatory effects have subsided, he presents a fairly clear-cut picture of damage to the brain stem on the right side with possibly some involvement of the cranial nerves in their intracranial peripheral portions on this side.

DR. OSCAR SUGAR: I am surprised that the patient is still alive. As you know, it is necessary only to pass a fine needle into the medulla oblongata during a cisternal puncture for the patient frequently not to recover. In this case, a 4-inch (10-cm.) knife blade passed through the foramen magnum, and the patient is still alive.

DR. JOSEPH A. LUHAN: It did not injure the medulla very much. Presumably, the blade scraped the lateral rostral portion of the medulla and entered the pons, and then it was twisted over a little. The blade was twisted.

DR. ROBERT L. TENTLER: The blade was completely curled up. Apparently, it went inside his skull, and the attacker pulled it out. There were no signs in the roentgenogram of fracture of the skull.

DR. PERCIVAL BAILEY: I think that it is not a good idea to bandage the eye of a patient who has paralysis of the fifth and seventh cranial nerves.

DR. ROBERT L. TENTLER: I did not know the lids had been unsutured. Formerly, when he tried to feed himself, he would put his finger nail into the cornea. The lids were sewn together.

DR. PERCIVAL BAILEY: He will wear his cornea off against the gauze.

DR. ROBERT L. TENTLER: There is not much left now.

Joseph A. Luhan, M.D., President, in the Chair

Regular Meeting, March 13, 1951

Ocular Palsies Associated with Diabetes Mellitus. DR. LEO A. KAPLAN.

A review of the literature on ocular-nerve paralyses associated with diabetes mellitus reveals that, although they are not uncommon, there is no unanimity of opinion as to the pathogenesis. Reference is made to neuritis, neuronitis, vascular changes in the vasonervorum, hemorrhage or thrombosis in the intramedullary portion of the brain stem, and mechanical pressure by arteriosclerotic vessels. Pathologic studies in the past have shown evidence of indentation of the sixth nerve by arteriosclerotic vessels of the brain stem with or without complicating diabetes mellitus. Dissociated third-nerve involvement and loss of normal lid-closure synkinesis suggest the possibility that hemorrhage in the brain stem is most likely the responsible factor when this nerve is involved. The absence of conjugate paralysis in sixth-nerve involvement strongly favors an infranuclear lesion.

Involvement of each of the three oculomotor nerves has been described, and, less frequently, that of the fifth, seventh, and eighth cranial nerves. In most cases evidence of associated vascular disease, such as hypertension, albuminuria, changes in the retinal vessels, and hemiplegias, is present. In three of the four cases reported here the patients had not known they were diabetic until the paralyses developed. In three cases the abducens nerve was involved, and in one case evidence of an alternating hemiplegia was presented. In two cases there had been previous involvement of the seventh cranial nerve peripherally. In the fourth case there was incomplete involvement of the third cranial nerve.

DISCUSSION

DR. BENJAMIN BOSHES: Dr. Kaplan should be commended, not only for his paper but for the care with which he has worded the title. He speaks of the "ocular palsies associated with diabetes mellitus." That ocular paralyses are associated with this disease is well established. In a number of instances in which I have suspected diabetes mellitus, a glucose-tolerance test has been done. The curve showed a definite tendency to remain elevated for three or four hours. Some paralyses occurred in persons who were diabetic, but the cause was not diabetes. Concomitance of disease does not mean causal relationship. In two cases which I saw recently the presence of diabetes was definitely established. The subsequent course showed that the paralyses were due to metastatic tumor, in one case from the breast and in the other from a tumor in the liver, as revealed at autopsy. The presence of diabetes had led to a diagnosis of paralysis associated with diabetes, and in neither instance was the diagnosis correct.

DR. HERMAN CHOR: In some cases it would appear that the ocular paralysis cleared up rather promptly after specific diabetic treatment was instituted. Is there any definite correlation between the treatment and recovery?

DR. JOSEPH A. LUHAN: Although such ocular paralyses, in which presumably an arteriosclerotic process is involved, are rare with diabetes, it is important for us to know of their occurrence and to learn that eventual spontaneous recovery is usually to be expected. However, as Dr. Boshes has pointed out, it is possible for a diabetic patient to have a much more serious condition, such as a brain tumor, beginning with ocular paralysis, so that only by exclusion and the clinical course can the etiologic diagnosis be made.

DR. HERMAN CHOR: Improvement in the status of the diabetes in no way hastens the recovery of the paralysis. There appears to be no relation between the development of ocular paralyses and the duration or severity of the diabetes. The most probable mechanisms are mechanical pressure on the nerves by arteriosclerotic vessels and/or minute hemorrhages in the brain stem.

Cerebral Granuloma Due to Schistosoma Japonicum: Report of a Case. DR. JOSEPH J. REIDY.

The patient was admitted to the hospital for treatment of glaucoma.

In 1945, while in the Philippines, the patient had onset of complete left homonymous hemianopsia, vertigo, headaches, and anorexia. A subdural hematoma was suspected, and a mass was removed from the right occipital region. This tumor was later diagnosed as a granuloma due to infestation with the ova of Schistosoma japonicum.

The patient made a good recovery, but the left homonymous hemianopsia persisted. About five years after this operation, chronic, noncongestive glaucoma developed bilaterally, and some constriction of the right peripheral visual fields was noted.

Schistosoma ova were found in the stool on only two occasions, one to seven months after operation. Nine stool specimens, taken in the first three months of 1951, were negative for ova. The patient's eosinophil count at no time was over 10%, and at present is 7%.

The literature, in which are reported 51 cases of cerebral involvement with S. japonicum, was reviewed. The present case was previously reported by R. F. Perkins and A. Uihlein (Cerebral Schistosomiasis, *J. Nerv. & Ment. Dis.* **107**:207-219 [March] 1948). It is again presented because of the persistence and extension of the visual-field defects, the occurrence of glaucoma, and the question of present activity of the schistosomiasis.

DISCUSSION

DR. BEN LICHTENSTEIN (Slides).

DR. ALEX ARIEFF: This case shows the importance of considering the possibility of the appearance of sequelae long after the war.

This patient shows symptoms almost 10 yr. after the war because of an infestation received at that time. Because our soldiers were in so many theaters all over the world, we must be aware of various etiologic factors.

DR. M. BROWN: Can Dr. Reidy, from a study of the literature, tell us whether these lesions occur as multiple lesions of the brain and whether there is any curative effect from operation?

DR. JOSEPH J. REIDY: In most of the cases of cerebral granuloma the lesions were miliary. In only four or five was the granuloma similar to that described in the present case, and no curative operative procedure was suggested.

Cortical Control of Pupillary Dilatation in Cats and Monkeys. DR. WILLIAM C. WILSON.

It was found that cerebral-reflex pupillary dilatation follows adequate cortical and subcortical excitation of the (1) gyrus proreus, gyrus genualis, and gyrus subcallosus in cats, and (2) the cruciate gyrus (area 8) in the rhesus monkey. Partial denervation of the pupil in cats and monkeys by section of the sympathetic chain in some experiments, and by ciliary-ganglionectomy in others, led to the following conclusions: Frontal-lobe-reflex pupillary mydriasis in cats is due to active inhibition of parasympathetic activity; in monkeys, predominately to sympathetic activity. Response to the light reflex and a study of ciliary-ganglion action potentials before, during, and after stimulation of the frontal lobe substantiate the belief that the resulting mydriasis in cats is due to inhibition of parasympathetic tone. In addition, evidence indicates that centrifugal frontal-lobe fibers regulating the light reflex by active inhibition of parasympathetic activity pass through the hypothalamus to the Edinger-Westphal nucleus.

This research was begun in the medical research laboratories, Fort Knox, Ky., and is being completed at Elgin State Hospital, Elgin, Ill.

DISCUSSION

DR. H. C. VORIS: I can vouch for the painstaking way in which Dr. Wilson studied patients at Cook County Hospital with unilateral dilatation of the pupil due to head injury or other neurologic lesions. He carried out well-controlled clinical observations under conditions which many of us know are not ideal at times. It is known from clinical observation that a unilaterally dilated pupil which still reacts to light has a different significance than a dilated pupil which does not react to light. When Dr. Wilson first approached me with this problem, I must confess that I assumed that these two types of pupils represented varying degrees of third-nerve injury. He was able to prove by his clinical observations that this was not the case, even before he did this experimental work. Of course, when a dilated pupil does not react to light, pressure on the third nerve is not the only possible cause; on the other hand, if a dilated pupil does react to light, a third-nerve lesion may still be present.

DR. OSCAR SUGAR: There are several things I should like to know about the unequal pupils. Some time ago there appeared an article on the incidence of anisocoria in presumably normal members of Navy personnel. I wonder whether Dr. Wilson has any statistics on the occurrence of unequal pupils in patients with the more ordinary neurologic disorders.

What happened to the pupillary inequality when the pressure was released or the blood clot was removed? Did it disappear? In the monkeys, were other portions of the cortex stimulated? There is another visual field in the occipital lobe. Dr. Wilson did not say how he reached the hypothalamus, and whether he controlled the placement of electrodes by anatomic preparations.

DR. J. TARKINGTON: Was the stimulation done when the animal was awake or under anesthesia?

DR. WILLIAM C. WILSON: In answer to Dr. Sugar's last question: The cerebral exploration was carried out with a bipolar concentric needle-electrode fixed to a Horsley-Clarke stereotaxic apparatus. The brains were perfused, in situ, with dilute solution of formaldehyde U. S. P. (1:4), and the subsequently fixed tissue was sectioned at a thickness of 20 μ and stained according to the technique of Weil. Subsequent identification and plotting of excitatory foci were effected by routine methods.

In answer to the question concerning the follow-up observation of patients with a dilated pupil that reacted well to light and accommodation stimuli: Owing to their severity of injury, debilitation, and poor nourishment a large number of these patients died; however, it was found that in those who survived the anisocoria disappeared in three to four weeks.

In answer to the question concerning anisocoria in 5% of normal persons: In view of the fact that in most of the 450 patients with anisocoria the condition was due to acute head injury and that 5% of a normal group would not represent the chance of occurrence of such a large number of head injuries, I felt justified in suggesting that the anisocoria in most cases was due to the intracranial disturbance, particularly since those patients who recovered revealed no anisocoria after three or four weeks.

In answer to the question concerning the experimental results in the monkey: Cortical stimulation was limited to the frontal lobe, and the results indicated that reflex mydriasis, though on a reciprocal basis, was predominantly sympathetic. The reflex mydriasis in cats was predominantly due to inhibition of parasympathetic tone. Since the results found in man suggested that the cortical control was effected by the sympathetic system, the similarity of the mechanism operating in the monkey and that in man suggests that the mechanism changes with the ascent in the phylogenetic scale.

The effects of induced subdural hematoma on the pupillary response are currently being studied at Elgin State Hospital in an effort to classify the mechanisms operating in the cat and monkey and to correlate experimental results with the clinical findings in 450 cases of acute head injury with anisocoria.

DR. J. TARKINGTON: The previous work was performed under diallylbarbituric acid (dial®) anesthesia; however, current work is being carried on without anesthesia.

Mirror Movements: Report of Two Cases. DR. LOUIS BERLIN.

After some acquired lesions of the central nervous system, involuntary movements may be induced which indicate a mass synergic response. As an example, a hemiplegic patient may find that the paretic extremity is suddenly elevated as he yawns or that forceful contractions of the normal extremities are associated with uncontrolled movements of the opposite extremity. In postapoplectic chorea, this imitation of the voluntary movement by the impaired extremity is especially prominent.

Imitative, or mirror, movements, involuntary movements of one extremity when the opposite extremity undergoes voluntary movement, occur during the first few months of infancy. These may persist into adult life when there is a severe cerebral defect, as in cerebral palsy. Occasionally mirror movements are observed despite the absence of any gross neurologic sign. Thus, they were described with the skeletal anomaly of the Klippel-Feil syndrome as though they were incidental findings. In fact, they are alleged to be fully developed only in that syndrome. However, the Klippel-Feil syndrome itself is often associated with neurologic defects. On the other hand, mirror movements may occur independently of any bony anomaly and without notable cerebral deficiency. Yet careful examination reveals that the patient has an old, static cerebral lesion which produced some awkwardness of fine movements in childhood and that this impairment of motor function gradually diminished as he developed.

The two patients to be presented showed mirror movements dating from childhood. These movements gradually diminished as they grew up. Both patients had mild neurologic abnormalities.

The first patient, a white man aged 27, was said to have had a normal birth and early development. In kindergarten he was observed to be awkward, and later the movements of writing, working with tools, or using scissors were mimicked by the opposite hand. Ultimately, he learned to control these imitative movements and taught himself to perform rotatory movements with one hand while he performed vertical movements with the other. He had onset of grand mal seizures at the age of 24. He presented generalized hyperreflexia, but the reflexes on the left were brisker than those on the right. Ankle and patellar clonus were elicited on the left, and a Babinski sign was obtained bilaterally. The electroencephalogram was normal, but the oxyencephalogram showed the right lateral ventricle to be greatly dilated.

The second patient, a white man aged 20, had suffered delay in respiration at birth because of strangulation by the umbilical cord. His development was normal, but at about the age of 3 yr. he was seen to be awkward in handling his blocks. As he grew older, he observed that writing, working on machinery, or using a screwdriver evoked similar movements on the opposite side, especially if he made no effort to suppress these movements. Neurologic examination revealed mild paresis of the right side of the face of central type, hyperreflexia on the right, and abortive right ankle clonus.

DISCUSSION

DR. R. P. MACKAY: Does Dr. Berlin consider a lesion of the pyramidal tract a prerequisite to the mirror movements as he has described them? All of us are familiar with the so-called contralateral Babinski sign, in which the sign appears on the pathologic side on stimulation of the normal side. Perhaps there is a relation between mirror movements and the contralateral Babinski sign.

DR. JOSEPH A. LUHAN: How do these mirror movements differ from normally associated movements?

DR. LOUIS BERLIN: With reference to Dr. Mackay's question, let me explain my own confusion as to what constitutes the pyramidal system. According to the article of Denny-Brown (Denny-Brown, J.: Disintegration of Motor Function Resulting from Cerebral Lesions, *J. Nerv. & Ment. Dis.* **112**:1 [June] 1950), the motor effect of cortical ablation is not dependent merely on whether or not area 4 is ablated. Instead, motor impairment can result from lesions anterior to area 4, and he prefers to speak of degrees of motor impairment. I believe that pyramidal dysfunction, as represented by the Babinski sign and hyperreflexia, is always present. It is my impression that the additional presence of extrapyramidal lesions as in some cases of cerebral paralysis, tends to bring out the mirror movements more prominently.

In reply to Dr. Luhan's question, I believe that these movements do not differ fundamentally from associated movements. As a result of the release mechanisms, instead of fine, discrete unilateral movements, the movements are, rather, in the direction of a massive discharge, so that the more obvious associated bilateral movements assume the form of mirror movements.

This syndrome does not occur with spinal-cord lesions. The presence of an adductor response in the lower extremities represents a mass response, as against a discrete reaction that would occur with an intact central nervous system. Of course, the presence of mirror movements may represent a distintegration of function at a high level, and in that sense they are analogous to the mass reaction that occurs when the level of disintegration is at the spinal-cord level. However, since the lesion is at a high level, there is still considerable preservation of complex functions.

NEW YORK ACADEMY OF MEDICINE, SECTION OF OBSTETRICS AND GYNECOLOGY AND SECTION OF NEUROLOGY AND PSYCHIATRY, NEW YORK NEUROLOGICAL SOCIETY

Arthur V. Greeley, M.D., *Chairman, Section of Obstetrics and Gynecology, Presiding*

Joint Meeting, Feb. 21, 1951

SYMPOSIUM ON MARRIAGE COUNSELING

The Physician as a Marriage Counselor.

DR. SOPHIA J. KLEEGMAN.

Marriage counseling is that branch of education and guidance which helps the about-to-be-married, and those already married, in all phases of the husband-wife relationship, with emphasis on the psychobiologic aspects. It is both preventive and therapeutic, and its goal is the establishment of a stable marriage and a well-adjusted family. Its preventive aspects lie in sex education of the young and in the premarital interview. Its therapeutic purpose is to help persons already married to resolve conflicts which are on the conscious level, with the physician taking an active role as counselor, much of the psychotherapy being directive and all of it being restricted to the conscious plane.

The general practitioner meets most of these problems and therefore should acquire the necessary training to give adequate service in meeting this need. Deep-seated neuroses or serious emotional problems are to be referred to the psychiatrist, and the physician should acquire the experience necessary to differentiate between these disturbances and the simpler ones.

In far too many instances present-day premarital interviews begin and end with the taking of blood for the Wassermann test. This is deplorable, since most young people are inadequately prepared for marriage, approaching it with fears, anxieties, conflicts, and much misinformation. At the same time, they are eager for and need information on anatomy of sex, the physiology of coitus, and some of the common problems of adjustment to the husband-wife relationship.

This paper presented a suggested outline for a premarital consultation, consisting usually of two or three half-hour interviews. A careful history is taken, with particular inquiry into attitudes toward sex, marriage, and the family. The anatomy and physiology of sex are discussed; anatomical fitness and emotional readiness for marriage are ascertained, and contraceptive advice is given when requested. Indications and contraindications for dilation of the hymen were presented.

The therapeutic aspects of marriage counseling were then presented. Sexual problems discussed were (1) failure of the wife to achieve orgasm; (2) disparity of desire; (3) premature ejaculation; (4) dyspareunia; (5) fear of pregnancy or unsatisfactory method of contraception; (6) frigidity, and (7) infertility. In each case the common causes were presented, and methods of meeting these problems were discussed.

Education and reassurance are the keynotes of the premarital interview. The general practitioner is usually the first to be consulted, and it is well within his province to handle both premarital and postmarital counseling. He should be more aware of his unique opportunity to help people at the beginning of the two most important relationships—the husband-wife and the parent-child.

What Contribution Should the Clergyman Make to Marriage Counseling? Rev. Worcester Perkins.

When a couple come to be married, it is of importance to determine what general insight they have. It is important to know whether they are temperamentally suited to each other, whether they have a comparable background, and whether their religious attitudes are understood. The clergyman is not a psychiatrist, but must have training and clinical experience to recognize psychiatric symptoms and to refer the patient when necessary.

I tell the girl I wish her to have a complete pelvic examination and to inquire of her gynecologist for contraceptive instructions. The man is also requested to see his physician. There are some psychological and emotional experiences which I talk over with them if they are willing or refer if they are not. In regard to premarital relations, no judgment can be made on a general basis, but every case must be handled individually and decided on its own merits. I request the couple to return 10 days after marriage.

Concerning marriages of persons of different faiths, it must be ascertained that the one who changes his faith knows what he is doing, and is not doing so merely because of the desire to marry the other party. Often it is necessary to see the parents of the couple if parental objection is raised.

The matter of planned pregnancy is of real importance, and I suggest an interval of 10 mo. for adjustment before pregnancy is contemplated.

All religious instruction falls into its right place after rapport has been established.

If the suggestions I offer are not sympathetically received, I do not press the matter, but I decline to marry the couple.

In postmarital problems, the purpose of the interview is not to bring a man and wife together, but to ascertain whether greater spiritual and psychiatric insight is possible. Sex education is preventive therapy against calamities in later life.

Christ never spoke of religion; it was always the fuller life: "I am come that ye might have life, and that ye might have it more abundantly." The counseling task of a clergyman is to achieve this end, and is therefore the work of religion on its highest level.

A Psychiatric Evaluation of Marriage Counseling. Dr. Robert W. Laidlaw.

The practice of marriage counseling, as distinguished from that of psychiatry as a whole, deals with interpersonal relationships in which problems relating to marriage are handled by a short-term, conscious-level approach. The counselor regards the "marriage," rather than either partner, as the patient. Both husband and wife, if they are actively seeking help, may be carried by one therapist rather than by two.

Because of the relatively simple techniques, properly trained and personally qualified persons in professional fields other than that of clinical psychiatry, such as psychology, sociology, social service, theology and education, may function as marriage counselors. Training for nonpsy-

chiatric counselors is being given at the Marriage Council of Philadelphia, and the Menninger Foundation is expanding its program to include clinical training for such counselors. The Veterans Administration is including training facilities for marriage counseling in its program for residents in psychiatry.

The nonpsychiatric counselor must be skilled in recognizing when a problem is beyond his depth and should be referred to a psychiatric colleague. It is important to recognize that most psychiatric training does not prepare the psychiatrist for marriage counseling. Emphasis has been on psychopathology rather than on the essentially normal person.

Claims made by marriage counselors regarding therapeutic results from a surface level and a short-term approach may seem open to question but are well authenticated. In contrast to the tenacity with which the psychoneurotic person clings to his symptoms, the symptoms born of ignorance and faulty sexual conditioning in the essentially normal person are most easily dislodged. Faulty sex techniques are often blamed by the lay person for sexual maladjustments, whereas the experienced counselor knows it is faulty attitudes which play the most important role.

Marriage counseling must be mindful of its limitations, but the psychiatrist who is interested in this field is in a unique position for service. His greater training enables him to deal with complex emotional problems which may be discovered in seemingly simple situations, and he may select whatever approaches are appropriate to the developing clinical situation.

The psychiatrist owes a debt of gratitude to his nonpsychiatric colleagues in the field of marriage counseling. They are doing a real work in preventive medicine.

DISCUSSION ON PAPERS PRESENTED AT SYMPOSIUM

DR. RICHARD N. PIERSON: It is a happy coincidence that this meeting should occur on the birthday of Robert L. Dickinson. He was the great advocate of all this kind of work. Dr. Dickinson was a great philosopher; he was a prophet, I am sorry to say, somewhat "without honor in his own country." There are many doctors who worked with him and learned from him, but it was the clergymen and the psychiatrists, more than the men in gynecology and obstetrics, who really were inspired by him and from whom he received great support. Dr. Dickinson believed in the happiness of human beings, as well as in their health. In our great centers we spend many dollars and large amounts of working-time in research on cancer, developing skill in complicated operative procedures, and yet how much time do we spend on marriage counseling?—an effort that may determine the happiness or the tragedy of a family. After all, there are many more babies in the world than cases of cancer, and I think that the happiness and health of the family are more important than any single clinical condition in the individual.

First, I should like to speak about Dr. Kleegman's delightful and complete presentation of her experience with marriage counseling. I shall mention one or two things that I did not hear her discuss. One is the time the girl comes for premarital examination. It is the general experience that she comes very late; she has all the excitement of the engagement, and then at the last moment her friends or her mother persuades her to come to us. She does not come soon enough. She comes a week, or two or three days, before the marriage. Dr. Laidlaw has described how he will spend four hours in careful talk and physical examination. It takes time to teach such excited youngsters the facts and to talk things out, and one cannot do that if one sees a tired girl only a few days before she is to be married.

Another point concerns the dilation of the hymen. I am sure the self-dilation method is an excellent one and can often be used. In a certain number of instances operation is required, and there, again, is the advantage of seeing the patient earlier, so that she can be wholly well before she is married.

Another consideration has to do with the type of girl who is hyperesthetic. She is what Cragin used to call a hothouse primipara. She cannot stand the ordinary contacts of life, particularly contacts which have to do with sex. These are the girls who are in my experience the most difficult to help in marriage counseling. They are the ones that have the most marked dyspareunia and are likely to have the most difficulty in their marriage adjustment. Many such youngsters are spoiled and misinformed. They expect the doctor to provide them with absolutes —methods of birth controls that are perfect and cannot fail. They say, "My period is due on

such a day, and I am being married on such a day, can't you give me something to postpone my period?" I say, "Who do you think I am—King Canute?" It is important for them to know that even the best doctors are not as bright as that!

I am impressed by Dr. Perkins' saying that he turned down more marriages than he performed. I give him great honor for taking such a position, and I think we doctors ought to take that point of view. We will not be stubborn and narrow-minded, I hope, about such things. However, if the patient is unable to understand or accept fundamental facts and principles of marital adjustment, it is not wise for the doctors or clergyman to agree to their marraige. We should educate ourselves and the laity to this point of view.

DR. ABRAHAM STONE: For those who have been in marriage counseling for many years, it is a great pleasure to find that these sections have joined for the first time tonight in presenting the subject of marriage counseling before the Academy of Medicine. The subject has two aspects: The first is that of providing information to the couples who come for counsel, and the second is concerned with attitudes, because, as Dr. Laidlaw has well said, and as Dr. Dickinson has insisted time and again, two things are involved in the marital problem, and the greater of the two is the attitude. Sometime a young person becomes imbued with an attitude long before he or she knows the actual facts of life or sex. Marriage counseling is curative and preventive. The latter aspect has been stressed by Dr. Kleegman, in emphasizing proper sex education, premarital counseling, and going to a minister, so that the couple may avoid difficulty later on. I insist that one or two hours, or 12 hr. spent with a counselor before marriage is worth a month, or a year, or three years, after marriage. It is the preventive aspect that marriage counselors are working on at present.

DR. ISABEL BECK: In the course of 20 yr. of marriage counseling, I have noted a decided change in the attitude of young people toward marriage. This is particularly true of young women who have had the advantage of the premarital courses which are given at various colleges. Some of these courses cover a wide range of subjects related to the field of marriage. They do an admirable work. They have helped give these girls insight into the psychosexual relations of marriage.

DR. PAUL LOEWY: The so-called psychogenic impotence is "psychogenic" in the sense of being acquired only partially by factors of family and social environment. However, the main etiologic factor in this kind of impotence is a constitutional familiohereditary one, comprising a specific set of autonomic psychoreflexes or, to define it more exactly, a specific set of "psychoautonomic" reflexes, with vasomotor and with visceromotor effectors, among them the unstriated, and in part even striated, vasomotor and visceromotor muscles of the sex organs. The sexual reactions belonging to this group are the reflex chains of ejaculation, of lubrication, of erection, and of an erection-suppressor reflex, which I call "deturgescence reflex." I found these reflexes hyperactive in about 1,000 men, from 22 to about 50 yr. of age, who came as patients either to be treated or to be advised concerning their sexual disturbances. They were also hyperactive in patients who came for quite different reasons, because of noncentral, i. e., peripheral neurologic diseases or for neuroses, and in an overwhelming number of persons, not patients, nonclinical or subclinical, whom I met everywhere. This group of people are to be diagnosed on first impression by three signs, in three contact-making situations: i. e., in making contact (1) with women; (2) with competitors or would-be competitors, or rivals or would-be rivals; (3) with a group, in being exposed to it as a single person.

One then finds the following syndromes: (1) excessive blushing, (2) sweating of palms, axillae and plantar surfaces, (3) typical motor and postural patterns of shy and self-conscious young men (sex timidity, rival timidity, and group timidity).

On neurological and psychiatric elaboration, one finds many more, and very important, neurological, behavioral and anamnestic signs. I emphasize especially the heredofamilial finding of brothers and fathers displaying the same syndrome as the observees or patients. This triad of "first-look" signs just mentioned (social and sexosocial blushing, palmar sweating, and timidity behavior) is a diagnostic guidance syndrome of relative test character and of extreme importance for marriage counseling. Comparative studies of dominance, submission, and sex behavior of animals contribute much to the understanding of this guidance syndrome of sex-reflex evaluation. I refer to a forthcoming publication.

PHILADELPHIA PSYCHIATRIC SOCIETY

Hugo Mella, M.D., *President in the Chair*

March 9, 1951

Two Hundred and Seventy-Seven Narcoanalytic Studies: Clinical and Theoretical Implications. Dr. Fritz A. Freyhan, Farnhurst, Del.

The study concerns a series of 277 narcoanalytical sessions involving 231 patients given during the period 1944 to 1950. The case material consisted of 71 patients with schizophrenia; 30 patients with manic-depressive psychosis, 16 patients with a paranoid condition; 20 patients with involutional psychosis, 14 patients with alcoholic psychosis, 16 patients with organic psychoses, 15 patients with psychoneurosis, 22 patients with psychopathic personalities, and 27 patients with personality disorders, without psychosis. Interpretative criteria had to be found to permit a differentiation of the diverse responses. The selected criteria concerned the following factors: 1. Orientation, pertaining to the state of ordered consciousness. Two modes can be differentiated: The patient maintains contact with the surrounding, or he goes into a twilight state. 2. Facilitation, referring to establishment of contact with previously inaccessible patients. 3. Affectivity, referring to changes in emotional tone. 4. Psychodynamics, pertaining to the dynamic value of the revealed thought material. As applied here, it stands for the expression of suppressed or repressed material. 5. Negativeness, referring to sessions which did not demonstrate any noticeable change.

All sessions were rated according to the selected criteria. The total results indicated an absence of exclusive correlations between diagnostic categories and type of responsivity. The significance of the total findings was discussed with respect to number of cases, diagnostic classification and response groups. Various examples of response types were given to illustrate essential points of differentiation. A number of repeated sessions were included in order to show similar and dissimilar responses in the same subject. The implications of these findings are as follows: Individual variation emerges as the dominating observation. There is no indication of conformity of responses to fixed patterns. No evidence could be found to suggest an intrinsic relation between depth of narcosis and the deeper levels of the personality.

The need for basic interpretive criteria was stressed in an effort to promote interest in comparative studies with narcoanalytical procedures.

DISCUSSION

Dr. Herbert Freed: This paper is stimulating and provocative, but with several points I am in complete disagreement. There is danger of confusion in the use of the words "dynamics" and "psychodynamics." They do not have the same meaning for everyone who uses them. We all are interested in and aware of the psychodynamics of the patient. We frequently fail to take into consideration the psychodynamics of the therapist. In this paper mention is made of psychodynamics as one of the criteria. In every dictionary "dynamics" is defined as the moving forces of one sort or another, as the term is usually applied in physics or chemistry, frequently in the sense of forces opposing each other. In each patient we are interested in the individual and in the environment of the individual. In narcoanalysis there is actually no dynamics, since the relationship between the patient and the therapist is nonexistent, except in cases in which the patient assaults the therapist.

I remember a patient whom I studied and treated in orthodox analysis for a few years. I had diagnosed his illness as ambulatory schizophrenia. He had been raised in foster-homes and had never had a chance to make any real identification with anyone. In the course of a few years this patient had made some progress but not enough. He had little affective lability. He always came up smiling no matter what happened to him. I gave the patient about 100 sessions of narcoanalysis. One of the interesting things in the early sessions was that there was no change in his behavior, except that he became more drowsy. There was no particular change in his emotional lability. Very soon in the course of these treatments the patient noticed that he had begun to take on some of the characteristics of the therapist. He began to identify with

me and take on some of my personality traits. In the course of therapy the patient did make some changes as a result of identification with the therapist. After only a few attempts nothing could be appreciated in the course of the therapy.

Dr. Freyhan attempts a statistical study of the reactions of a number of patients during one or more narcoanalytic sessions. As far as I am concerned, these statistics have no psychiatric significance because they are based on the responses of the individual subject under narcohypnosis. When the subject is in a state of narcohypnosis, there is no interpersonal relationship. Unless the statistics concern two people—the patient and the therapist—they have practically no psychiatric significance. Such evaluation would be as sterile as looking through the entire population for your so-called "normal" person.

Dr. Fritz A. Freyhan, Farnhurst, Del.: I appreciate Dr. Freed's comments. I was afraid of misunderstanding on this point, although I had hoped to express my thoughts clearly. If one takes as the object of one's study the immediate results of a great number of sessions, as I did, one cannot go into the deep analytic relationships. The object of this study was not to talk about interpersonal relationships, but to discuss the dynamics of the group in general and the appreciable changes which one psychiatrist, who sees the patient every day, can observe, and by the aid of which he can define his situation under narcoanalysis. I did not emphasize one detail or one case. I should have done that—gone from one case to the next. My object simply was to find out what can be learned from a series of analyses of the general population of a large psychiatric hospital made under narcohypnosis, in an effort to determine the general validity of the method.

The term "dynamics" has a very strong emotional connotation. We say of someone who seems lacking in emotional response that he is not dynamic. I feel it is a matter of semantics and emotional attitudes rather than of scientific clarity. Every change is dynamic. To be precise, "dynamic" must have a specific meaning. I wanted to find out in how many of these instances a narcoanalytic session added to my knowledge. Consequently, I do not think it is the duty of an investigator who reports on as large a series as this to include in his study the relation of the physician to the patient, with which we are all acquainted, but which has no particular bearing, I feel, on the object of this study.

If I did not make clear that I was after the general response patterns, I am guilty of all the things Dr. Freed emphasizes.

Obesity—A Psychiatric Evaluation of Fifty Obese Women. Dr. Albert J. Kaplan, Dr. Baldwin L. Keyes, and Dr. Robert Bookhammer.

The authors evaluated the psychiatric status of 50 obese women who were studied at the endocrine clinic of the Jefferson Medical College Hospital. (These studies were part of a research project in which obesity was being studied from the clinical, social, anthropological, and psychological points of view.) All patients had previously been examined to rule out the presence of any gross organic disease associated with their obesity. The method used was that of an approximately one-hour psychiatric interview.

Forty-five, or 90%, of the patients in this study were considered neurotic. The outstanding symptoms were those referable to eating and disturbances in the psychosexual sphere. Most of the patients in this group became obese during the child-bearing period, and pregnancy was the commonest precipitating factor. Most of the women were mid-siblings; often the mother was obese. The economic status of this group of patients was poor, and parental separation and conflict during childhood were frequent.

Five cases were briefly reported to point up a few of the superficial psychological patterns discernible in one interview; these included indulgence, rejection, passive dependence, repressed hostility, emotional immaturity, and regression in the face of stress, such as pregnancy or operation. The authors emphasized that the psychological dynamisms that prevail in obesity are as numerous as in any neurosis, and that deeper studies give a more profound and meaningful view of the psychodynamic forces underlying obesity. These include basic concepts, such as incorporation, introjection, identification, oral dependence, castration fear, homosexuality, narcissism; sadomasochism, oral-pregnancy fantasies, influence of body image, mania or depression, and other defenses.

It was the authors' opinion that obesity in most instances is a neurosis that is most likely to occur in persons of a particular constitutional type and that it is characterized by overeating, the accumulation of fat, and various neurotic symptoms.

DISCUSSION

DR. EDWARD WEISS: Obesity, as the authors have indicated, has become an important public health problem as we have learned to recognize the high incidence of cardiovascular-renal disease among persons who are overweight and, of course, the increased mortality rate in this group. It is also interesting that obesity, like peptic ulcer, is now one of the best recognized psychosomatic disturbances, and the time may not be far away when one obese person on meeting another will inquire, not "How are your glands?," but "How is your psyche?"

Because obesity was formerly considered a problem of endocrine glands and calories, injection of various hormones, as well as very severe restriction of calories, has been a common principle of treatment. Now, as Dr. Kaplan and his associates point out, obesity is regarded as more than a matter of calories; it is a matter of family background and of attitudes, as well as situational factors. In other words, when obesity runs in families, habits are as important as genes; and in this regard pseudoheredity becomes as important as heredity, and by that I mean the family setting in which obesity occurs.

Bruce made a study of obesity in children and the feeding problem in a family setting. In many cases in which the mothers were overanxious about the welfare of their children, the affection of these neurotic mothers for their children was a thin veneer for an underlying insecurity in dealing with them, and they would often stuff the child with food instead of giving him affection. As a physical basis for obesity, we have found persistent inactivity in these obese children, and the child characteristically satisfies his need for entertainment in movies, comic books, and comic strips. Such a child has had few opportunities for creative expression and has tended toward emotional immaturity. The family is represented by a weak and unaggressive father and a domineering mother, who has herself often had an unhappy childhood. Over half the children were unwanted. In only a few families was the marital relationship satisfactory. Usually the mothers were cruel and unreasonable in discipline, and yet were overindulgent in feeding. Food had an exaggerated importance. While eating, the child had a sense of security. In general, activity and social contacts came to be associated with a concept of insecurity and danger. All through the literature, the psychological aspects show the linkage to the instinctive development of the gastrointestinal function. As Dr. Kaplan has pointed out, insecurity and the feeding experience, or anxiety tied up with it, have usually laid down patterns with a gastrointestinal reaction, which would be awakened much later in life. One sees these early regressive features in persons who gluttonously rush to the icebox and fill themselves with food, often without realizing what they are doing. Even in numerous middle-aged families whose members have become obese, and whom the general practitioner usually sees, the nagging sensation in the epigastrium, often characterized as nervous hunger, is symbolic of the emotional impotence of these persons; and so they try to fill this void with food because they lack emotional satisfaction.

We have found that the incidence of emotional disturbances in the clinic patients is very high, and it is difficult to pick out a trial group when studying any psychosomatic disturbance. In the outpatient population, one must be aware of the fact that a large number of factors act as artefacts in the incidence of neuroses in the patients one is studying. I agree with Dr. Kaplan that one must do more than restrict calories and give amphetamine or glandular extracts. We must help these patients to grow up, so that they can achieve satisfaction in some other way than by stuffing themselves with food. In treating obese people by various means, it has been found that the best and most lasting results are obtained in those people who have psychotherapy in addition to restriction of food or treatment by drugs.

DR. BALDWIN KEYES: Dr. Kaplan and Dr. Weiss have thoroughly covered the subject from the standpoint of the problem, its etiology and the suggested therapy. They fail to find a specific common denominator. They seem to be certain that there is a common denominator in the early response to emotional need. Someone has suggested that while waiting for therapy, we might teach these fat women to smoke cigars.

We have carefully avoided discussing the fat man; he belongs in this picture also. It is very necessary that this kind of investigation be continued. In the continuance of this study, we must emphasize more and more that physicians other than psychiatrists, particularly pediatricians, should be interested in this problem. Treatment must begin before these patients become fat men and women. Mental hygiene offers our best opportunity to arrest the neurosis before the patient needs such careful psychotherapeutic aid.

DR. ALBERT J. KAPLAN: I would like to underline Dr. Weiss's remark on the social implications of obesity. Newburgh stated that after the age of 40 there is a 25% increase in mortality for each 25% increase in weight. It seems as though there is something deeply destructive in overeating that evidences itself in the way in which it follows a course in which many diseases are encountered. This is an interesting subject in itself. Most diabetic patients are overweight, and many are profoundly neurotic. There is another relationship—that of the thin and the obese, the alcoholic and the obese, the addict and the obese. The $64 question seems to be: "What about the persons who are fixated early, but who are neither thin nor obese." That is to say, there seems to be a constitutional factor, and it must be due to something not known at present.

Impotence. DR. SAMUEL A. ZERITSKY.

Male sexual potency may be defined as the ability to initiate, sustain, and conclude satisfactorily the fact of sexual intercourse to the satisfaction of the male. Impotence is a symptom of aberrant function and not a disease per se. The disorder may be partial or complete, temporary or permanent. It may be relative to the patient's wife, with no impairment in cohabitation with other women. Difficulties starting with a tendency to premature ejaculation almost always end in failure of erectile power.

There are comparatively few cases in which the impotence is entirely on an endocrine basis. Serious pathologic changes may be present in the lower genitourinary tract without any disturbance in sexual potency. The commonest cause of interference with potency is anxiety, which may be conscious or unconscious. Successful masturbation, nocturnal emissions, and morning erections are all prima-facie evidence of innate potentia and indicate that the disorder is one of psychological impotence. Penis neurosis will be manifested by psychosexual disturbance, and the mechanisms involved will exhibit regression or fixation on the oral, anal or, phallic level. The syndrome is based on unresolved incestuous attachment, unconscious in scope, accompanied with an unconscious fear of aggression, that is, the possibility of castration by the father.

The case was presented of a veteran, now 25, who married when he was 19. During the week of his honeymoon he failed completely to have an erection. Several months later, while being visited by his wife at an Army camp, they spent several days together, but he was again impotent. Upon his return from overseas, 11 mo. later, he joined his wife, but even with hormone injections he remained impotent, and she divorced him.

The veteran, in describing his sexual development, denied ever having indulged in masturbation, had never experienced sexual intercourse prior to marriage, and had made no attempt to engage in sexual activities since his divorce for fear of again proving to be impotent. He asserted that he got frequent erections and had periodic nocturnal emissions. Although, by physical examination, it was noted that he had unusually small testes, he presented all the secondary characteristics of the male.

While various operative procedures, the use of aphrodisiacs, alcohol, hormone injections, and even mechanical apparatus for coitus-training, have all been mentioned as useful in the treatment of impotency, the vast majority of patients will require a prolonged course of psychotherapy.

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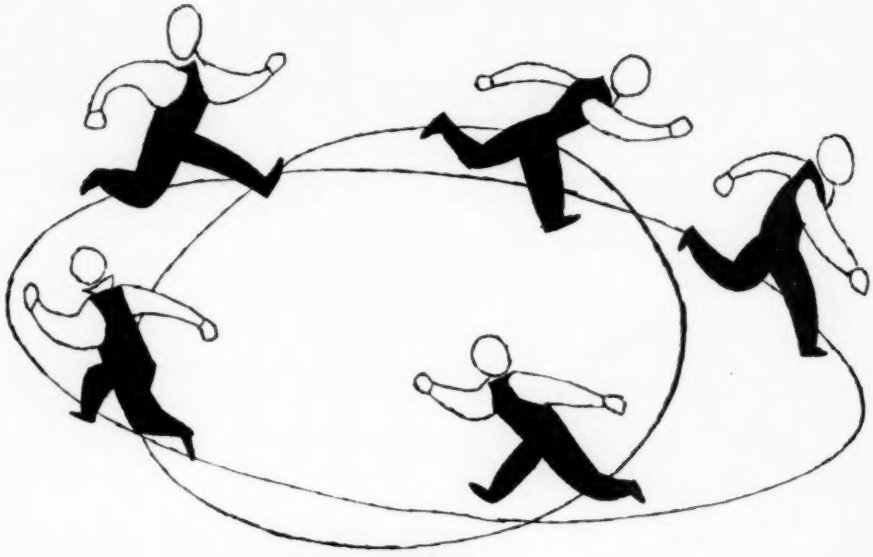

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